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MECHANISM OF PRODUCTION OF ACIDOSIS IN PREMATURE INFANTS BY PROTEIN MILK

WILLIAM S. HOFFMAN, M.D., Ph.D.
ARTHUR H. PARMELEE, M.D.
AND
AARON GROSSMAN, M.D.
CHICAGO

IN A PRECEDING paper[1] electrolyte balance studies were carried out on premature infants who were on a diet of diluted evaporated milk and "dextri-maltose." The results demonstrated that these infants tended to retain small quantities of chloride in excess of the sodium required for the formation of new extracellular fluid of normal composition. Consequently, the serum chloride concentration was somewhat higher than that of normal adults or of full term, breast-fed infants, and the serum carbon dioxide content was slightly lower. The serum sodium levels tended to be on the low side of normal. However, these infants did not have any recognizable difficulties as a result of this condition. Their growth was normal, and they remained in good health. After several weeks, the serum chloride tended to return to a lower level.

The present paper deals with the effect of a diet of protein milk powder on the acid-base balance of premature infants and on the distribution of water and electrolytes in the fluid compartments of the body. The investigation offers corroboration of the observation of Darrow and his colleagues[2] that a diet of protein milk powder is capable, in three days, of producing a profound acidosis, with dehydration, loss of weight, elevation of serum chloride levels and reduction of serum bicarbonate concentrations. To determine the role of the kidney in the development of this acidosis, cation-anion partitions were made of the twenty-four hour excretions of urine. Furthermore, in order to ascertain whether prematurity was the important factor, similar studies were carried out on full term infants.

From the Hektoen Institute for Medical Research and the Children's Division of the Cook County Hospital.

1. Hoffman, W. S.; Grossman, A., and Parmelee, A. H.: Electrolyte Balance Studies on Premature Infants on a Diet of Evaporated Milk, Am. J. Dis. Child, to be published.

2. Darrow, D. C.; Da Silva, M. M., and Stevenson, S. S.: J. Pediat. 27:43, 1945.

METHOD OF STUDY

The procedure for the collection of the urine and the method of analysis of food mixtures, urine, stools and serum were identical with those described in the preceding paper.[1] Preliminary balance studies were carried out on 3 "normal," premature male infants who were placed on a diet of powdered protein milk[3] for three days and whose urine and stools were collected and analyzed in the same manner as that of the 15 premature infants given the evaporated milk diet described in the previous paper.

For the study of the cation-anion partitions of the urine the plan of investigation was as follows: Male premature infants who had been doing well on a diet of evaporated milk were placed on an accurately analyzed evaporated milk diet for three days. This portion of the study was called the control period. Collections of urine were made for each twenty-four hour interval under aseptic conditions in small bottles containing toluene. Each twenty-four hour specimen was analyzed immediately for the various cations and anions, as well as for nitrogen. At the end of three days, blood was drawn under oil for serum analyses. Then the infants' diet was changed isocalorically to one of powdered protein milk suspended in distilled water. Collections of urine were again made for three twenty-four hour periods, and each twenty-four hour sample was analyzed immediately. At the end of three days, blood was again drawn for serum analyses. This procedure ended the powdered protein milk period. The infants were then returned to the original evaporated milk diet for a recovery period of three days during which twenty-four hour samples of urine were again collected and analyzed. A final specimen of blood was drawn at the end of the recovery period. Food mixture aliquots of both diets were analyzed for the minerals and nitrogen. Unfortunately, stool analyses were not carried out during these special studies of the urine. A total of 5 premature and 3 full term infants were submitted to these experiments.

PRELIMINARY BALANCE STUDIES ON PREMATURE INFANTS

Table 1 shows the balances obtained in 3 premature infants who were placed on a diet of powdered protein milk for three days without any preliminary control study. Comparison of these balances with those obtained with evaporated milk in the previous investigation shows that a negative balance of sodium resulted instead of a positive one. The balances of all the other mineral constituents were positive. They were smaller than those obtained for evaporated milk because in these infants, our first on powdered protein milk, the diet chosen was inadvertently too low in calories. To the subjects utilized later for the special urine studies, from 30 to 50 per cent more powdered protein milk was administered. In the latter infants greater positive

3. The powdered protein milk used in these experiments was furnished us by Mead Johnson and Company, Evansville, Ind. It represented material withdrawn from sale when the work of Darrow and his colleagues showed its excess of chloride. The product was made by precipitation of casein with calcium chloride and the addition of the casein to whole milk, according to a method recommended by Finkelstein. The mixture was then evaporated to a powder. The powdered protein milk now offered for sale has been modified to avoid the excess of chloride.

balances were obtained, but the negative balances of water and sodium were also greater. However, these three preliminary experiments served to corroborate Darrow's observations. The results of serum analyses demonstrated that in three days a serious acidosis developed in these infants, as indicated by a pronounced increase in serum chloride concentration and a fall in the serum bicarbonate content. The serum sodium concentrations were at low normal level.

TABLE 1.—*Three Day Balances for Premature Infants on a Diet of Protein Milk Powder*

	Chloride, mM	Sodium, mM	Potassium, mM	Phosphate, mM	Calcium, mM	Fat, Gm.
Intake	23.7	10.0	20.6	27.4	38.5	
Urine	20.6	16.4	13.0	13.2	6.5	
Stool	0.8	0.2	5.6	7.1	18.4	11.01
Balance	2.3	—6.8	2.0	7.1	14.6	
Intake	21.3	9.0	18.5	24.7	34.7	
Urine	13.7	11.8	14.2	10.7	7.0	
Stool	0.9	0.2	3.9	5.1	24.7	9.93
Balance	6.7	—3.0	0.4	8.9	3.0	
Intake	23.7	10.0	20.6	27.4	38.5	
Urine	19.3	12.0	11.9	7.2	5.3	
Stool	0.8	0.2	1.7	5.0	16.0	4.74
Balance	3.6	—2.2	7.0	15.2	17.2	

Table 2 gives a comparison of the average serum electrolyte concentrations in the 15 premature infants on the evaporated milk diet with the concentrations in the 8 infants on a diet of powdered protein milk for three days (3 infants in the preliminary balance study and 5 in the special urine studies). It can be seen that the mild chloride acidosis obtained with evaporated milk was profoundly exaggerated by the diet of powdered protein milk. The bicarbonate fell to less

TABLE 2.—*Comparison of Average Serum Electrolytic Concentrations for Premature Infants on Powdered Protein Milk with Concentrations for Infants on Evaporated Milk*

Diet	Number of Infants	Chloride, mEq./L.	Sodium, mEq./L.	Potassium, mEq./L.	Phosphate, Mg./100 Cc.	Calcium, mEq./L.	Bicarbonate, mEq./L.
Evaporated milk	15	110	141	5.5	7.5	5.8	18.8
Powdered protein milk	8	116	136	5.3	7.7	5.5	12.0

TABLE 3.—*Urine Partition Studies on Infants on Three Three-Day Regimens Before, During and After Powdered Protein Milk Diet*

Case No.	Diet	Volume, Cc.	pH (Average)	Total Nitrogen, Gm.	Ammonia, mEq.	% Nitrogen as Ammonia	Titratable Acidity, mEq.	Organic Acidity, mEq.	Inorganic Sulfate, mEq.	Phosphate, mEq.	Chloride, mEq.	Total Acid, mEq.	Sodium, mEq.	Potassium, mEq.	Base Economy, mEq.	McCance Factor
4 Premature	Control	342	5.60	1.89	10.7	8.0	11.3	13.1	6.2	21.2	18.8	59.5	11.8	22.2	25.5	398
	Powdered protein milk	639	5.89	3.91	14.9	5.3	11.9	16.3	11.3	30.0	26.8	84.4	27.6	20.2	36.5	344
	Recovery	549	6.16	3.67	25.0	9.5	11.2	12.8	9.5	28.1	26.3	76.7	15.9	20.7	40.1	368
5 Premature	Control	369	5.58	1.74	10.4	8.4	13.7	26.0	5.0	20.7	22.9	74.4	16.4	22.0	36.0	377
	Powdered protein milk	465	5.90	3.24	20.7	9.0	10.5	14.5	8.0	25.3	23.8	71.6	17.5	18.6	35.6	391
	Recovery	411	5.93	2.70	16.3	8.5	11.9	12.3	4.5	25.0	23.6	65.3	11.2	19.4	34.7	392
6 Premature	Control	451	5.59	2.18	3.6	2.3	8.8	10.9	7.1	10.7	18.7	47.4	13.8	22.6	11.0	328
	Powdered protein milk	834	4.96	5.00	8.0	2.2	19.9	14.0	13.0	19.9	24.0	70.9	28.9	14.6	27.4	291
	Recovery	843	5.07	3.91	17.6	6.3	15.7	12.1	6.9	17.5	31.6	68.1	17.0	27.4	23.8	273
7 Premature	Control	729	5.40	1.94	5.1	3.1	10.0	11.9	4.8	12.6	22.2	51.5	19.4	28.2	3.9	218
	Powdered protein milk	840	—*	2.50	—	—	—	13.6	4.4	11.1	18.7	47.7	18.1	22.9	6.7	194
	Recovery	603	—*	2.84	—	—	—	14.5	5.5	11.4	19.0	50.3	10.4	18.3	21.6	260
8 Premature	Control	477	5.07	1.79	4.0	3.1	11.4	9.0	2.5	11.3	16.3	39.0	13.3	18.5	7.4	258
	Powdered protein milk	585	4.96	3.90	14.3	5.1	13.4	15.1	6.9	14.6	16.7	53.3	23.9	10.1	19.9	325
16 Full term	Control	741	5.12	4.18	12.8	4.3	17.6	13.5	9.5	18.2	34.4	75.6	31.4	30.3	13.9	351
	Powdered protein milk	825	5.05	5.33	20.0	5.2	18.3	17.6	12.3	18.2	24.1	72.3	36.5	20.4	15.4	331
	Recovery	588	—*	3.38	—	—	—	17.7	8.3	14.4	17.8	58.2	11.3	15.9	31.0	289

TABLE 3.—Cont.—*Urine Partition Studies of Infants on Three Three-Day Regimens Before, During and After Powdered Protein Milk Diet*

Case No.	Diet	Volume, Cc.	pH (Average)	Total Nitrogen, Gm.	Ammonia, mEq.	% Nitrogen as Ammonia	Titratable Acidity, mEq.	Organic Acidity, mEq.	Inorganic Sulfate, mEq.	Phosphate, mEq.	Chloride, mEq.	Total Acid, mEq.	Sodium, mEq.	Potassium, mEq.	Base Recovery, mEq.	McCance Factor
17 Full term	Control	546	5.75	2.80	7.7	3.8	13.1	15.0	6.7	15.0	21.6	52.3	13.7	20.5	12.2	306
	Powdered protein milk	621	5.17	4.55	14.2	4.4	14.9	15.4	11.5	15.8	19.8	56.6	19.7	12.7	18.2	340
	Recovery	642	—*	2.87	—	—	—	18.5	7.3	14.1	26.1	61.0	8.9	19.2	27.9	257
18 Full term	Control	585	5.72	4.03	9.3	3.2	17.1	16.1	9.4	48.2	28.0	101.8	20.0	40.9	40.9	443
	Powdered protein milk	660	—*	5.56	—	—	—	27.7	17.1	45.2	31.6	120.6	25.7	22.2	73.0	426
	Recovery	363	—*	4.29	—	—	—	31.7	8.5	47.0	28.2	115.4	11.5	18.1	85.8	590

*Specimens of urine were alkaline because of the presence of a urea-splitting organism.

than half of its normal concentration. The average serum sodium level was lower than normal. On the other hand, there was no appreciable variation in the concentrations of serum potassium, calcium or phosphate.

The excretions of fat in the stools of the infants on powdered protein milk were variable, but in none were the high values found that Darrow obtained. These lower values may have been due to the limited caloric intake of the infants. The infants on evaporated milk showed the same variations.

URINE PARTITION STUDIES

In table 3 are given the cation-anion partitions of the urine of 5 premature male infants during a nine day period—three days of an evaporated milk control diet, three days of the powdered protein milk diet and three days of recovery on the original evaporated milk diet. (One subject [case 8] became severely ill at the end of the powdered protein milk period and had to be withdrawn from the metabolic study before the recovery period could be instituted.) The results given are the total for each period, even though the analyses were made on each twenty-four hour excretion sample. The *p*H is the arithmetical mean for each three day period. In each of these infants by the end of the powdered protein milk period a typical clinical picture of dehydration and acidosis had developed, with depression of the anterior fontanels, poor cutaneous turgor, Kussmaul breathing and generally poor appearance. The serum analyses (table 4) confirmed the clinical observations. During the recovery period the symptoms rapidly disappeared, even though chemically restitution to normal was not complete.

The volume of the urine was seen to increase in each twenty-four hour excretion during the protein milk diet. In 2 instances (cases 4 and 6) it was almost doubled. Since the fluid intake was practically constant for each infant for each three day period and since the environmental temperature was constant, the urinary loss should represent, for the most part, the loss of weight if the urinary loss was entirely due to loss of water. Actually, the loss of urine of each infant was much greater than the loss in weight, which apparently meant that some of the loss of water was made up for in the gain of tissue substance. The increased urinary output persisted in 3 of the 4 infants during the recovery period.

The *p*H of the urine for most of the infants lay between 5 and 6 during the control periods. The interpretation of the changes in acidity that occurred during the study is complicated because of a peculiar, inexplicable contamination that developed in several speci-

mens of urine. In spite of every precaution to keep the collecting apparatus sterile, and in spite of a layer of toluene in the collecting bottle, the specimens, as each study progressed, tended to become alkaline because of a urea-splitting organism in the urine. This phenomenon seldom occurred during the control period, but it was not infrequently present on the second or third day of the protein

TABLE 4.—*Chemical Analyses of the Serum in Premature and Full Term Infants Before, During and After Diet of Powdered Protein Milk for 3 Days*

Case No.	Diet	Chloride, mEq./L.	Sodium, mEq./L.	Potassium, mEq./L.	Phosphate, Mg./100 Cc.	Calcium, mEq./L.	Bicarbonate, mEq./L.	Protein, Mg./100 Cc.
4 Premature	Control	115	138	4.7	6.5	5.4	16.0	
	Powdered protein milk	119	135	5.3	7.2	5.7	10.7	
	Recovery	114	140	4.8	6.0	5.2	13.8	
5 Premature	Control	109	139	5.8	5.4	4.5	26.7	
	Powdered protein milk	118	136	4.7	7.1	5.0	11.6	
	Recovery	112	138	6.5	5.9	5.1	20.9	
6 Premature	Control	109	141	5.4	9.0	5.1	18.3	5.09
	Powdered protein milk	117	133	5.0	7.5	5.9	12.5	5.09
	Recovery	112	136	6.1	8.0	5.6	20.6	4.94
7 Premature	Control	111	139	5.7	6.7	6.0	20.8	5.00
	Powdered protein milk	112	136	4.4	7.1	6.3	15.1	5.26
	Recovery	111	139	5.2	6.0	6.3	18.3	4.81
8 Premature	Control	110	139	5.6	8.3	5.9	19.0	4.75
	Powdered protein milk	118	133	5.3	7.8	5.5	12.5	5.81
	Recovery	—	—	—	—	—	—	—
16 Full term	Control	107	138	6.2	7.2	5.7	21.0	5.50
	Powdered protein milk	112	134	5.9	7.8	5.4	16.1	6.13
	Recovery	115	135	4.3	6.3	5.1	20.5	6.19
17 Full term	Control	105	142	5.6	9.8	5.6	25.9	5.38
	Powdered protein milk	108	139	5.3	7.8	6.2	22.8	5.74
	Recovery	107	142	5.7	9.0	6.2	25.0	5.25
18 Full term	Control	108	140	5.5	8.0	6.5	20.5	5.81
	Powdered protein milk	114	138	6.5	7.0	6.6	13.8	5.88
	Recovery	114	139	5.4	6.0	6.5	16.9	5.88

milk period or during the recovery period. Because of this disturbing complication a number of balance studies had to be abandoned altogether. Others were carried through to completion, with a recognition that the values for *pH*, titratable acidity, ammonia and, possibly, organic acids were incorrect. The phenomenon occurred in every attempt to perform balance experiments on the full term infants, even

when they were kept under the strict asepsis of the station for premature infants. For that reason, the protocols of urine acidity for the full term infants have to be interpreted with reserve.

The cause of the contamination was not determined. It could not have been the collecting bottle, since that always contained a large quantity of toluene. The rubber cot and the collecting tubing were always freshly autoclaved before being attached; a new apparatus was used each day. There was no recognizable stasis in the tubing. On two occasions freshly passed urine direct from the urethra showed the same high *p*H and ammonia content as that in the bottle. Escherichia coli was isolated from these specimens. There was no fever or any sign of sepsis, but these infants did show the distress, the rapid breathing and the blood chemical picture of acidosis. The most reasonable hypothesis was that in the presence of acidosis saprophytic bacteria from the urethra were allowed to pass retrogradely into the bladder and thus to set up bacterial growth in the bladder urine. The tendency was probably caused or aggravated by the constant presence of the collecting apparatus.

Those specimens which obviously had high alkalinity, high ammonia content and low or no titratable acidity are so indicated in table 3. Other specimens in which changes were not so obvious might have had such contamination, especially if both the *p*H and the ammonia content were higher than the values for the control specimens. Nevertheless, in 2 infants (cases 6 and 8) true and consistent urinary acidities were almost certainly present in all specimens. We believe the observations on these infants are representative of the true state of affairs in this series of experiments.

In 1 infant (case 6), the average *p*H of 5.59 became reduced to a level of 4.96 during the powdered protein milk period, a value near the lower limit of *p*H observed in adults. During this period the titratable acidity was more than doubled, as was the production of ammonia. In the recovery period, the *p*H returned to a slightly higher level. The titratable acidity remained high. The excretion of ammonia was almost five times that of the control period, which allowed a large excretion of chloride and other acids with a saving of fixed base. In the other infant (case 8) similar results were obtained. The *p*H of the urine, already at the low level of 5.07, became 4.96 during the protein milk period. At the same time the titratable acidity increased, but ammonia increased to an even greater extent.

The absolute increase in ammonia during the protein milk period undoubtedly was due partly to the greater intake of nitrogen. The percentage of total nitrogen as ammonia did not show so great an increase as did the value for absolute ammonia, but in 1 infant (case 6) at least even this percentage increased.

The excretion of ammonia during the control period was less than the titratable acidity, a condition regarded by Van Slyke and associates[4] as indicating limited ability to produce ammonia. However, under the stress of acid excretion, the quantity of ammonia formed became greater than the titratable acidity; but this increased production was delayed and did not reach the maximum until the recovery period, even as was observed in adults by Linder.[5]

Base Economy.—The quantity of base that can be spared in the excretion of acids is measured either by the sum of the titratable acidity and the ammonia or by the difference between the total anions and the total fixed base.[6] The former group comprises sulfate, phosphate, chloride and organic acids. Each of these anions can be measured with reasonable accuracy, with the exception of organic acids, the values for which by the commonly used method of Van Slyke and Palmer[7] are approximations. In addition, creatinine and possibly other organic compounds in the urine may serve as bases. Since the excretion of creatinine was observed to be constant in these infants (between 0.2 and 0.3 milliequivalent) and represented only a negligible amount of base, and since calcium, and presumably magnesium, was also relatively constant and insignificant, the base economy could be calculated without much error as the difference between the sum of organic acids, sulfate, phosphate and chloride and the sum of sodium and potassium. The values determined by this method should be of the same order as that for the sum of titratable acid and ammonia. In a number of instances the agreement was good. In the cases of decided disagreement, the discrepancy was probably due chiefly to the error in determining organic acids. Nevertheless, the base economy calculated by difference can be used as an approximate measure of the changes instituted in the urine during the stress of the developing acidosis and during recovery. In addition, its determination makes possible a description of the changing pattern of the excretion of the individual acid and base. Furthermore, such a determination can be of use even in the presence of contaminated urine.

In the powdered protein milk period 3 infants (cases 4, 6 and 8) showed an increase in the total acid excretion which involved not only chloride but also sulfate and phosphate. In another infant (case 5) sulfate, phosphate and chloride were likewise increased, but the value for total acids did not show this increase because the excretion of

4. Van Slyke, D.D.; Linder, G. C.; Hiller, A.; Leiter, L., and McIntosh, J. F.: J. Clin. Investigation **2**:255, 1926.

5. Linder, G. C.: Quart. J. Med. **20**:285, 1927.

6. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 647.

7. Van Slyke, D. D., and Palmer, W. W.: J. Biol. Chem. **41**:567, 1920.

organic acids was diminished. Only in 1 infant (case 7) was there no increase at all in excreted acids, which can be accounted for by the low protein diet given this subject (table 5). With the increase in the excretion of acid—which was to be expected, since the infants during this period were on a high protein diet—the base economy increased. In spite of this increase, extra amounts of fixed base were lost in the urine. Moreover, the loss of base was confined entirely to sodium. In fact, the excretion of potassium decreased during the development of acidosis, and this retention of potassium was at the expense of further loss of sodium. Thus, although less sodium was

TABLE 5.—*Dietary Intake of Infants in Urine Studies for Three Day Period*

Case No.	Infant	Type of Milk Diet	Quantity, Gm.	Chloride, mM	Sodium, mM	Potassium, mM	Phosphate, mM	Calcium, mM	Nitrogen, Gm.	Water, Cc.
4	Premature	Evaporated*	450	31.9	25.1	40.4	32.1	34.6	4.46	1,440*
		Powdered protein*	120	29.7	12.4	25.8	34.2	48.2	5.64	1,440*
5	Premature	Evaporated	450	31.9	25.1	40.4	32.1	34.6	4.46	1,440
		Powdered protein	130.5	32.2	13.5	28.0	37.2	52.4	6.14	1,440
6	Premature	Evaporated	540	38.3	30.3	48.5	38.6	41.5	5.35	1,710
		Powdered protein	150	37.0	15.5	32.2	42.8	60.2	7.05	1,710
7	Premature	Evaporated	540	38.3	30.3	48.5	38.6	41.5	5.35	1,620
		Powdered protein	105	22.5	10.9	22.5	30.0	42.1	4.94	1,620
8	Premature	Evaporated	540	38.3	30.3	48.5	38.6	41.5	5.35	1,710
		Powdered protein	150	37.0	15.5	32.2	42.8	60.2	7.05	1,710
16	Full term	Evaporated	630	44.7	35.0	56.6	44.9	48.4	6.24	1,800
		Powdered protein	180	44.4	18.6	38.6	51.4	72.2	8.46	1,800
17	Full term	Evaporated	630	44.7	35.0	56.6	44.9	48.4	6.24	1,800
		Powdered protein	180	44.4	18.6	38.6	51.4	72.2	8.46	1,800
18	Full term	Evaporated	900	63.8	50.4	80.8	64.2	69.2	8.91	2,430
		Powdered protein	240	59.2	24.8	51.5	68.5	96.3	11.28	2,430

*All infants were offered 1 ounce (30 cc.) of weak tea between feedings. All evaporated milk feedings included 15 Gm. "dextri-maltose" for the three day period.

available from the diet during the ingestion of protein milk, more sodium than before had to be lost to bring about the excretion of the large quantity of acids. This loss accounts for the negative balance of sodium. The decreased excretion of potassium was due partly to the diminished intake of the base and also partly, as we shall explain, to the retention of potassium in the tissue cells.

During the recovery period, acid excretion remained elevated. Now, however, since more ammonia was produced and since more potassium was made available for excretion, the loss of sodium could be diminished. A positive sodium balance could thereby be established.

These observations on an infant (case 6) are graphically illustrated in the chart.

Molar Concentrations of the Urine.—One of the striking features of the urinalyses of all these infants was the relative constancy of the concentration of the constituents analyzed. If the significance of this observation had been realized at the time, determinations of specific gravity and estimations of freezing point might have been undertaken. Isolated specimens did show specific gravities from 1.006 to 1.012. From the data that we have available it is possible to get some estimate of the variability of the molarity of the specimens of urine by making calculations based on the McCance molarity factor. This factor is

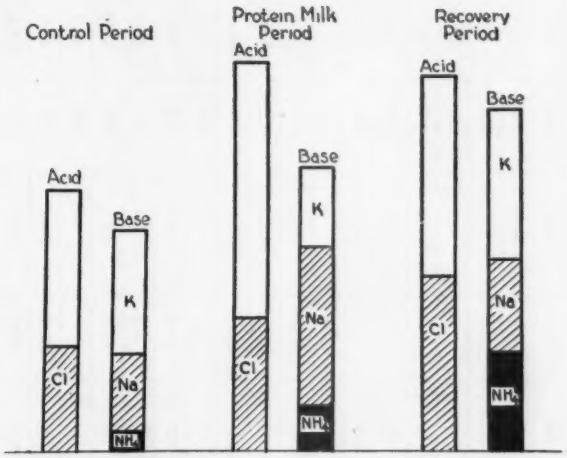

Chart showing changes in base economy in an infant (case 6). Bars represent urinary excretion of total anions and total fixed base in the control, the protein milk and the recovery periods. Clear portions of acid rectangles indicate sulfate, phosphate and organic acid content.

$$\frac{\text{mM urea} + \text{mM chloride} + \text{mM sodium} + 2\ \text{mM potassium}}{1{,}000\ \text{cc.}}$$

Young, Hallum and McCance[8] found that this factor is a measure of the osmotic pressure of the urine. The millimols of urea were estimated by assuming that 90 per cent of the total nitrogen excreted was urea nitrogen. The data in table 3 in the column headed "McCance Factor" show a constancy through all three periods for each subject and not too great a variation among the 5 subjects. The range is from 194 to 398. Furthermore, if the molarity of serum is similarly calculated, a value of about 270 is obtained. McCance and Young[9] have already shown that adults under stress of limited water

8. Young, W. F.; Hallum, J. L., and McCance, R. A.: Arch. Dis. Childhood **16**:243, 1941.

9. McCance, R. A., and Young, W. F.: J. Physiol. **99**:265, 1941.

TABLE 6.—*Distribution of Water, Sodium and Chloride in Diets of Evaporated Milk and Powdered Protein Milk in 5 Premature and 3 Full Term Infants*

Case No.	Regimen	Weight, Gm.	Balances			Extracellular Content			Intracellular Balance	
			Water, Gm.	Chloride, mM	Sodium, mM	Water, Gm.	Chloride, mM	Sodium, mM	Water, Gm.	Sodium, mM
4 Premature	Start	1,978	—	—	—	495	56.9	70.3	—	—
	Control	2,064	86	12.5	13.1	544	69.4	76.5	37	6.0
	Powdered protein milk	1,909	—155	2.2	—15.4	542	71.6	74.6	—153	—13.5
	Recovery	1,930	30	5.0	9.0	605	76.6	86.5	—33	—2.9
5 Premature	Start	2,115	—	—	—	529	60.8	75.1	—	—
	Control	2,129	14	8.4	8.5	572	69.2	81.1	—29	2.5
	Powdered protein milk	2,043	—86	7.7	—4.2	587	76.9	81.4	—101	—4.5
	Recovery	2,171	128	7.7	13.7	680	84.6	—	+35	—0.7
6 Premature	Start	2,256	—	—	—	564	64.9	80.1	—	—
	Control	2,370	114	18.9	16.3	699	83.8	97.2	—15	—0.8
	Powdered protein milk	2,356	—14	12.3	—13.6	740	96.1	100.0	—61	—16.4
	Recovery	2,441	85	6.0	13.1	821	102.1	113.9	+4	—0.8
7 Premature	Start	2,264	—	—	—	566	65.1	80.4	—	—
	Control	2,285	21	15.4	10.7	653	80.5	92.7	—66	—1.6
	Powdered protein milk	2,270	—15	3.1	—7.4	672	83.6	93.3	—34	—8.0
	Recovery	2,342	68	15.6	19.7	805	99.2	114.2	—65	—1.2
8 Premature	Start	2,200	—	—	—	550	63.2	78.1	—	
	Control	2,256	56	21.3	16.8	692	84.5	98.1	—86	—3.2
	Powdered protein milk	2,156	—100	19.6	—8.6	795	104.1	105.0	—203	—15.8
16 Full term	Start	3,249	—	—	—	812	93.4	115.3	—	—
	Control	3,405	156	8.9	+3.2	861	102.3	121.2	107	—2.7
	Powdered protein milk	3,207	—198	18.9	—18.3	975	121.2	133.3	—312	—30.4
	Recovery	3,349	142	25.5	23.3	1175	146.7	157.5	—27	—0.9

TABLE 6.—*Distribution of Water, Sodium and Chloride in Diets of Evaporated Milk and Powdered Protein Milk in 5 Premature and 3 Full Term Infants—Continued*

Case No.	Regimen	Weight, Gm.	Balances			Extracellular Content			Intracellular Balance	
			Water, Gm.	Chloride, mM	Sodium, mM	Water, Gm.	Chloride mM	Sodium, mM	Water, Gm.	Sodium, mM
17 Full term	Start	3,973	—	—	—	993	114.2	140.8	—	—
	Control	4,058	85	21.7	20.9	1165	135.9	168.9	—87	—7.2
	Powdered protein milk	3,803	—255	23.2	1.5	1327	159.1	188.2	—417	—20.8
	Recovery	3,859	56	17.2	25.7	1484	176.3	215.0	—101	—1.1
18 Full term	Start	3,434	—	—	—	858	98.7	121.8	—	—
	Control	3,491	57	34.4	30.0	1110	133.1	158.5	—195	—6.7
	Powdered protein milk	3,207	—184	26.2	—1.1	1259	159.3	177.1	—333	—19.7
	Recovery	3,207	0	34.2	38.5	1529	193.5	216.8	—270	—1.2

can increase the molar concentration of the urine to three times that of the serum, whereas premature infants cannot concentrate the urine to any extent above that of the plasma.

Our data indicate a comparable result for these premature infants. Thus, it is recognizable that the premature infant succeeds in excreting excess waste products only by increasing the output of urine and that the limitation of this excretion is the amount of water available for the formation of urine.

DISTRIBUTION OF WATER AND ELECTROLYTES IN BODY FLUIDS

The experiments involving urinary partition of cations and anions were not primarily intended for balance studies. Therefore, analyses of stools were not carried out. However, the sodium and chloride content of the stools of the premature infants on whom balance studies were performed was so uniformly low that the utilization of the average excretion of sodium and chloride in the stool of these 18 infants would involve little error. The average values were 0.2 millimol of sodium and 0.7 millimol of chloride per three days. Thus, with the knowledge of the intake of these subjects (table 5) it was possible to estimate the balance of sodium and chloride in the body water and to calculate the distributions of these substances in the fluid compartments by the use of Darrow's method. With Darrow and associates,[2] we made the following assumptions:

1. The volume of the extracellular fluid of the normal baby at the beginning of the experiment equals 25 per cent of the body weight.
2. Chloride is distributed only in the extracellular fluids not merely under normal conditions but also in abnormal states, such as acidosis.
3. Gain or loss of weight during the short period of the study represents gain or loss of body water.
4. The concentration of chloride and sodium in the extracellular fluid is measured by the concentration of serum chloride and sodium if correction is made for the weight of water in a liter of serum, that is, $\times$ 100/94, and for the slightly altered distribution of chloride and sodium as a result of Donnan's membrane equilibrium, that is, $\times$ 100/96 for chloride and $\times$ 96/100 for sodium. Thus, if we assume, as Darrow did, that the initial serum chloride and sodium levels were 104 and 139 milliequivalents, respectively, then

Extracellular chloride concentration = $104 \times 100/96 \times 100/94 = 1.11 = 115$ mEq. per kilogram of water.

Extracellular sodium concentration = $139 \times 96/100 \times 100/94 = 139 \times 1.02 = 143$ mEq. per kilogram of water.

5. Muscle, which constitutes about 40 per cent of the infant's body, is the chief repository of intracellular water and easily shiftable sodium and potassium.

These assumptions are far from quantitatively valid, but the errors involved are probably not great enough to invalidate the qualitative observations based on them. The data shown in table 6 were developed from such calculations in the same manner as were Darrow's data. From these values the following conclusions are manifest for the 5 premature infants (cases 4 to 9 inclusive):

1. The volume of extracellular fluid usually expanded in all three periods. Even in the powdered protein milk period, when dehydration was present, the volume of extracellular fluid was at least equal to that in the control period for 1 infant (case 4) and was somewhat greater for the other 4 infants. In the periods when there was a gain in body water, part or all of the increase in extracellular fluid came from this gain in body water; the rest came from intracellular water. In the protein milk periods, since body water was also lost, both this loss and the increase in extracellular fluid came from muscle intracellular water. This value is shown as a negative balance for water in the column headed "Intracellular Balance."

2. The positive balance of sodium during the control period was usually sufficient to neutralize the retained chloride without the need of any appreciable shift from the intracellular compartment, as indicated by a small positive or an insignificantly negative balance of sodium in the intracellular column. However, during the period of severe acidosis, when the concentration of extracellular chloride increased markedly, the negative body balance of sodium apparent in these periods forced sodium from the cells, some to be lost in the urine, the rest to neutralize the retained chloride. Otherwise, the acidosis would have been even severer. This result is seen in the large negative balances for sodium in the intracellular column.

3. During the three day recovery period, there was a large positive body balance of sodium in all the infants. This retained sodium stopped the transfer of sodium from muscle. However, not enough sodium was retained to restore that lost from the cells during the previous period.

Our data on the 5 babies used for urine studies do not permit a calculation of balance and distribution of potassium, for the fecal potassium was found to be too variable and too large to permit an average value to be chosen. However, calculations on the three preliminary balance studies shown in table 7 (cases 1, 2 and 3) point to the retention of sufficient quantities of potassium to allow an increase in intracellular potassium at the time of loss of intracellular sodium. The retention of these infants was small because the intake was too meager. However, our urine studies offered further corroboration. It was seen that the excretion of potassium was diminished during the powdered protein milk periods. If fecal excretion was not much

TABLE 7.—*Balances and Distribution of Water and Electrolytes in Premature Infants on Diet of Powdered Protein Milk*

Case No.	Regimen	Balances				Serum				Extracellurar Content				Intracellular Balance		
		Water, Gm.	Chloride, mM	Sodium, mM	Potassium, mM	Chloride, mM/L.	Sodium, mM/L.	Potassium, mM/L.	Bicarbonate, mM/L.	Water, Gm.	Chloride, mM.	Sodium, mM.	Potassium, mM.	Water, Gm.	Sodium, mM.	Potassium, mM
1	Start	(Weight	1,965	Gm.)						491	56.7	69.6	2.2			
	Powdered protein milk	—21	2.3	—6.8	2.0	117	138	5.8	10.6	454	59.0	64.0	2.6	16	—1.3	1.6
2	Start	(Weight	1,873	Gm.)						468	54.0	66.3	2.1			
	Powdered protein milk	—28	6.7	—3.0	0.4	117	141	5.0	9.9	467	60.7	67.2	2.3	—27	—3.9	0.2
3	Start	(Weight	2,185	Gm.)						546	63.0	77.4	2.5			
	Powdered protein milk	—85	3.6	—2.2	7.0	111	139	6.4	12.9	542	66.6	76.8	3.4	—81	—1.6	6.1

altered during this period, good positive balances of potassium must have occurred. Furthermore, since the potassium content of extracellular fluid showed insignificant changes, even with increases in the volume of fluid, the bulk of any positive balance must have gone to the cells. Some of this increase in potassium was no doubt associated with the growth of muscle tissue, but, as Darrow calculated, there was a residual amount of potassium that was related to the phenomenon of decrease in muscle sodium.

STUDIES ON FULL TERM INFANTS

In order to determine whether acidosis would develop in full term infants when they were placed on a diet of protein milk powder, 7

TABLE 8.—*Serum Electrolyte Concentrations in Full Term Infants Before and After Three Day Period of Powdered Protein Milk Diet*

Case No.		Weight, Gm.	Chloride, mEq.	Sodium, mEq.	Bicarbonate, mEq.
9	Before	3,640	106	140	22.3
	After	3,610	114	132	8.9
10	Before	3,520	105	137	19.2
	After	3,370	108	137	18.8
11	Before	3,520	111	142	22.8
	After	3,370	111	135	14.3
12	Before	3,260	104	138	20.5
	After	3,230	108	137	16.0
13	Before	3,610	108	140	22.8
	After	3,460	111	134	17.9
14	Before	3,580	103	143	23.2
	After	3,460	103	141	23.0
15	Before	3,550	105	143	17.8
	After	3,460	106	141	17.5

infants were given such a diet, isocaloric with their previous diet of cow's milk. These infants were all normal "boarders" in the Children's Hospital and ranged in age from 7 to 11 days. Blood was drawn for serum analyses at the beginning and at the end of the three day period of protein milk diet. The serum concentrations are shown in table 8. Of the 7 infants, a severe acidosis developed in only 1 (case 9), but 4 others showed moderate symptoms of acidosis. For these infants, the serum chloride level was elevated, the sodium level was depressed and the bicarbonate concentration was appreciably lower than the previous level. In 2 infants (cases 14 and 15) there were no significant changes in the serum electrolytes. Thus, it appeared that

full term infants are susceptible to the acidotic effects of a protein milk diet but that the acidosis engendered is not so severe as in premature infants.

To elucidate if possible the metabolic differences in these more mature infants, urine partition studies similar to those on the 5 premature infants were undertaken on 3 full term infants. There were three days of evaporated milk control diet, three days of an isocaloric powdered protein milk diet and three days of recovery on the original evaporated milk diet. Acidosis developed in the infants while they received the protein milk, but their symptoms and the alterations in the serum were not so severe as those of premature infants. The serum levels listed in table 4 show a moderate fall in the bicarbonate concentration and a rise in that of chloride. The sodium levels were slightly depressed. During the three days of recovery, the chloride levels were not appreciably changed, but sodium and bicarbonate concentrations increased. Clinically, the infants improved rapidly. Serum potassium, phosphate or calcium showed no significant changes.

Unfortunately, it was impossible to study the changes in the production of acidity and of ammonia in all periods in these 3 infants. The decomposition of the urine described previously occurred in all three recovery periods and in at least one of the protein milk diet periods (table 3). Two infants (cases 16 and 17) gave patterns for acidity and production of ammonia that were consistent for the first two periods. In both periods there was a slight fall in the average *p*H in the protein milk period, with increased titratable acidity and a considerable rise in production of ammonia. As in the case of the premature infants, even though economy was affected by an increased excretion of ammonia and titratable acid, the quantity of sodium that had to be excreted was increased, while potassium was retained. During the recovery period, the base economy was still greater (presumably from a further increase in production of ammonia) and more potassium was available for excretion. Consequently, there was good storage of sodium.

The excretion of ammonia in the control samples was less than the titratable acidity, but with the development of acidosis the former equaled or surpassed the latter, indicating the ability of the infant to produce ammonia under stress. The percentage of total nitrogen as ammonia appeared to be slightly greater than that for the premature infants.

One infant (case 18) had a much higher intake of food than did the other 2. His output of urinary constituents was expectedly greater than that of the others. However, the unusually large urinary output of phosphate and organic acids was difficult to explain. Since the excretions of sodium and potassium were not increased to the same

degree, the calculated acid-base differences were observed to be much greater than those for the other infants.

The volume of urine was increased during the protein milk period, but to no great degree. In fact, the quantity of water excreted during all periods for these larger infants was not much greater than that for the premature infants. Since the excretion of solids was much greater in the full term infants, the molar concentration must necessarily have been higher. The calculated McCance molarity factors showed that such an increase occurred. In 1 infant (case 18) the molarity was almost twice as great as that for some of the premature infants. In other words, these full term infants had a greater ability to concentrate the urine under stress than did the premature infants.

For the determinations of the balances of water, sodium and chloride for the full term infants and of the distribution of these constituents in the extracellular and intracellular compartments, calculations were made with the assumptions as for the premature infants, except that fecal excretions of sodium and chloride for each three day period were taken as 0.4 and 0.14 millimol, respectively. The data are shown in table 6. The results, on the whole, were equivalent to those for the premature infants. In the protein milk period, balances of water and sodium were negative, while chloride (and presumably potassium) was in positive balance. The retained chloride distributed only to the extracellular fluid produced an expansion of this fluid which required withdrawal of water and sodium from the intracellular compartment. During the recovery period extracellular fluid increased still further, but practically no sodium had to be shifted from the intracellular compartment. The essential difference observed for these full term infants lay in the small negative balance of sodium (at least for 2) and the greater ability to draw water and sodium from muscle.

COMMENT

Our results are in full agreement with the report by Darrow and his co-workers that a diet consisting entirely of unmodified protein milk powder has too great an excess of chloride for the premature infant to manage without the development of a chloride acidosis. Within three days the infants lost weight, showed a negative balance of water and sodium and demonstrated by clinical symptoms and serum chemistry the signs of severe acidosis. In fact, as Darrow anticipated, even in full term infants a similar acidosis developed, but of much less severe degree. Furthermore, even a diet of evaporated cow's milk has enough excess of chloride to produce in premature infants a moderate chloride acidosis, but it seldom interferes with health or growth. After some time, the infant appears to be able to dispose of

the extra chloride, so that the serum chloride concentration returns to normal.

An analysis of the inorganic composition of the diets of evaporated milk and of protein milk (table 5) shows other differences than merely an excess of chloride over calcium. For the same number of calories and approximately the same quantity of chloride, powdered protein milk contains much less potassium and much more phosphorus, calcium and protein nitrogen. Sulfate also is undoubtedly increased. Thus, in the catabolism of this dietary mixture there is an increased amount of phosphate and sulfate, with less sodium and potassium to neutralize these acids. Potassium is still less available for neutralization, since by being shunted into the intracellular compartment it is removed from the fluid reaching the kidney. The brunt, then, of neutralization of the increased excretable acid falls on sodium. Even without this burden there is not enough sodium to take care of the retained chloride, which has produced an expansion of extracellular fluid. Our data, as well as Darrow's, point to a withdrawal of sodium from muscle not only for new extracellular fluid but also for the neutralization of the excreted acid. Thus, the negative balance that ensues is entirely at the expense of intracellular sodium, and the amount of sodium and water from the muscle mass available for these purposes determines the extent of the rise in serum (or extracellular) chloride concentration and that of the fall in sodium and bicarbonate levels.

Our data on the cation-anion partition of the urine of the premature infants imply that the infant's kidney, in spite of its well recognized immaturity,[10] does respond, as the adult kidney does, to the stress of accumulation of acid in the body by the production of ammonia. As in the adult, the increased formation of ammonia is delayed, so that little use can be made of this phenomenon during the three day protein milk period. It is not until the recovery period that the ammonia synthesis provides a sizable saving of base. Unlike the normal adult, the ratio of ammonia to titratable acidity in premature infants is less than 1, a value which signifies some limitation in the production of ammonia. Even at the time of its maximal formation, the percentage of total nitrogen as ammonia nitrogen was still much less than that seen in adults with, for example, diabetic acidosis.

Though the ability of the premature infant's kidney to produce ammonia is limited, this limitation is not the cause of the special vulnerability to the protein milk diet. A more significant failing of the kidneys of these infants is their inability to concentrate the urine.

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10. Smith, C A: The Physiology of the New Born Infant, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 243.

Young, Hallum and McCance[8] showed that premature and full term newborn infants have low urea and inulin clearances. Furthermore, they demonstrated by cryography and by calculation of the molarity of the urine that infants cannot concentrate the urine to the same degree as adults. Our own studies corroborate these observations. The urine tended to contain the same concentration of each of its constituents under all regimens. Whatever increased excretion occurred was accomplished by a larger urinary output. This type of activity is similar to that seen in cases of renal insufficiency in chronic Bright's disease, in which the urine has a nearly fixed specific gravity. Only by making more water available for excretion can retention be diminished. This observation may account for the beneficial effect of clyses of 5 per cent dextrose solution or of isotonic solution of sodium chloride in these cases of acidosis in infants.

The full term infant does not differ greatly from the premature infant, but the aggregation of small differences apparently enables him to respond more effectively to the powdered protein milk diet. In the first place, the kidneys, having slightly greater maturity, are able to produce a more concentrated urine, and thus they succeed in conserving base a little better than the premature infant's kidneys. As a result, the negative balance of sodium is relatively smaller, and the relative retention of chloride is less. Second, relatively more water and sodium are available from muscle for the purposes of excretion and for the expansion of the extracellular fluid volume. Thus, the retained chloride is more readily diluted. Even with all this help, the full term infant is still unable to prevent a moderate acidosis.

Our data show that the excess of chloride in the powdered protein milk diet for the premature infant is approximately 15 millimols. This quantity is about one-fourth the total chloride content of the baby's body. The magnitude of this assault can be better visualized if the calculations are made in terms of the adult. A person weighing 70 Kg., with 20 per cent of his body as extracellular fluid, has 14 Kg. of fluid, the chloride concentration of which is about 115 milliequivalents per kilogram. If one fourth of this amount of chloride is given as ammonium chloride for three days, the dose will be more than 21 Gm., or 7 Gm. per day. Even in adults some degree of chloride acidosis will probably be recognizable after three days of such treatment.

In our calculations of the distribution of water and electrolytes between extracellular and intracellular fluids, we obtained corroboration of Darrow's results because we made the same assumptions as he did. It is not the purpose of this paper to argue the validity of these assumptions. However, we feel that the greatest possible error is the assumption that there is no chloride in intracellular water

either under normal conditions or under the conditions in which sodium is being extracted from the intracellular compartment. Yet, of course, without such an assumption this method of calculation is impossible. Another error is the assumption that loss of weight is equivalent to loss of water. This assumption is denied in the calculation of gain in muscle tissue from the nitrogen balance by means of which it is recognizable that even with the loss of weight there has been a gain in tissue. These and other possible errors may serve to vitiate fine conclusions drawn from the data. Nevertheless, the constant demonstration in all the protein milk experiments that the negative balance of water and sodium is associated with an increase in extracellular water and sodium, which could come only from intracellular fluid, is probably undeniably correct; so, too, is the conclusion that the extra potassium enters the cell in place of sodium. Darrow[11] utilized the same type of calculation to demonstrate that in the reverse condition, in which excessive chloride is lost and alkalosis is produced, extracellular sodium enters the cells to replace potassium which is lost in the urine. The validity of these calculations was established by the efficacy of clinical management based on restitution of the lost potassium and chloride. Furthermore, Darrow and Govan[12] applied similar methods of study in cases of diarrhea of infectious origin and showed the beneficial effect in such cases of replacement of water, chloride, sodium and potassium.

SUMMARY AND CONCLUSIONS

Studies of electrolyte balance and serum analyses made on 3 premature infants showed that a diet of unmodified powdered protein milk for three days produces a serious acidosis with elevated serum chloride and lowered serum bicarbonate levels. The balance of sodium and water is negative and the balance of potassium, calcium and phosphorus positive. These results are in corroboration of Darrow's observations.

Cation-anion partition studies of the urine on 5 other premature infants over a nine day period—three control days of evaporated milk diet, three days of protein milk diet and three recovery days of evaporated milk diet—demonstrated that the limited production of ammonia normally exhibited by these infants could be increased under the stress of acidosis, but that it did not reach its maximum until the recovery period. Titratable acidity and hydrogen in concentration were also increased. The chief renal limitation was the inability to concentrate the urine. In spite of the increase in base economy, there

11. Darrow, D. C.: J. Pediat. **26**:519, 1945.
12. Darrow, D. C., and Govan, C. D., Jr.: J. Pediat. **28**:518 and 541, 1946.

was a drain of sodium from the body to help neutralize the increased excretion of chloride, phosphate and sulfate. At the same time, less potassium was available for excretion.

Calculation of the distribution of electrolytes and water demonstrated that during the powdered protein milk period chloride retention usually produced an expansion of extracellular fluid volume. Since the balance of water and sodium was negative, these items had to be drawn from the intracellular fluid compartment for this expansion, even as Darrow had found. While sodium was being removed, the potassium content of cells increased. In the recovery period, the positive balance of water and sodium succeeded partly in reversing this process, but it was not sufficient to restore the lost sodium in muscle.

Acidosis also developed in 10 full term infants on the powdered protein milk diet, but to a less severe degree. Urine partition and balance studies on 3 of these infants showed that the essential differences between these and the premature infants lay (1) in the slightly more mature renal function, which allowed a greater excretion of chloride and a greater conservation of sodium, and (2) in a relatively greater reserve of water and sodium in muscle that could be drawn on to permit the expansion of extracellular fluid volume.

629 South Wood Street (12).

Dr. Philip Aries (premature infants section) cooperated in these studies. Miss Bess Osgood, Miss Thelma Garvin and Miss Gwen Stolzenburg assisted with the chemical analyses, while Miss Margaret Anderson and Miss Gwendolyn Boccio assisted with the care of infants, the collection of specimens and the preparation of food mixtures.

MYOCARDITIS AND PERICARDITIS IN MENINGOCOCCIC INFECTIONS

CHARLES UPTON LOWE, M.D.
AND
LOUIS K. DIAMOND, M.D.
BOSTON

CHEMOTHERAPY, by reducing the early mortality in meningococcic disease, allows the appearance of late complications. The 13 year old girl whose illness is reported survived the early days of her disease with the aid of chemotherapy, but severe cardiac complications developed. A review of the literature has failed to reveal reports of any other child in this age group with a similar complication who survived.

REPORT OF A CASE

A patient with meningococcic meningitis and meningococcemia was treated with sulfadiazine and penicillin. On the ninth day of illness a cardiac friction rub developed; pericardotomy revealed pericardial and myocardial lesions. Recovery occurred following prolonged illness.

History.—A 13½ year old white girl was admitted to the Children's Hospital on April 16, 1946, with a chief complaint of drowsiness, rash and pains in the joints. There was no family or personal history suggestive of rheumatic infection.

The present illness began seven days before admission when a transient rash, interpreted as hives, was noted on her face. The child had no complaints except as related to the eruption, and after twelve hours the rash disappeared. The following day she complained of a slight sore throat and felt chilly, but these symptoms subsided, and three days before entry she was seen by the family physician, who found her well. In the afternoon two days before admission, she started to vomit, and the next morning complained of soreness in her joints and on the flexor surfaces of her extremities. During the day before admission a severe headache developed, and petechiae were noted for the first time, most marked on the face and chest. There was no fever on several occasions when the oral temperature was measured. Twelve hours before admission the girl became delirious. Vomiting occurred as often as every two hours and continued up to the time of admission. On the morning of admission the petechial rash covered her whole body. She was drowsy and thirsty and complained of headache and considerable pain in her joints. A single specimen of urine passed two hours before admission was not remarkable in color.

Physical Examination.—On admission the patient was semicomatose and obviously severely and acutely ill. The temperature was 98.6 F., the pulse rate 120

From the Department of Pediatrics, Harvard Medical School, and the Children's and Infants' Hospitals.

and respirations 20. The blood pressure was 130 systolic and 80 diastolic. Two distinct types of lesions were noted on the skin. There were pinpoint, nontender petechiae which did not blanch with pressure. In addition, eight or ten large, blue-black, ecchymotic areas, 3 to 4 cm. in diameter, were noted on the arms, thighs and chest. These seemed tender to pressure. The chest was clear, and the heart not remarkable. The spleen was felt two fingerbreadths below the left costal margin. The neck was stiff, and there was a postive Brudzinski sign. Her joints seemed exceedingly tender to pressure, and there was some limitation of motion, particularly in the knees and elbows.

Fig. 1.—*A*, cutaneous lesions on the left thigh and left arm on the eighth day of hospitalization. Note necrotic centers of the irregular punched-out areas. *B*, skin in the same area six months later. Note good healing with moderate scarring.

Course.—A lumbar puncture was performed immediately after admission and yielded 25 cc. of cloudy fluid, which contained 22,900 polymorphonuclear cells per cubic millimeter, and 310 mg. of protein per hundred cubic centimeters. A smear revealed gram-negative diplococci, which on culture proved to be type I meningococci. Twenty thousand units of penicillin was instilled intrathecally, immediately, and sulfadiazine was administered subcutaneously initially, and by mouth thereafter. Blood culture taken at this time grew type I meningococci.

During the second and third days of hospitalization the patient's sensorium cleared markedly, and the headache diminished. The temperature remained normal. Because of pain in the right knee joint and a rise of temperature, penicillin was administered intramuscularly. A second lumbar puncture on the third day in the hospital showed considerable clearing of spinal fluid.

Those cutaneous lesions which had been large and ecchymotic at the time of admission had become necrotic on the fifth day of hospitalization (fig. 1A). At this time the patient's pulse rate had begun to rise slowly from 98 to 130, although the temperature remained normal (fig. 2). The heart sounds continued to be of good quality, no murmurs were heard, and no cause for the tachycardia was immediately apparent. Late in the evening of the seventh day in the hospital the

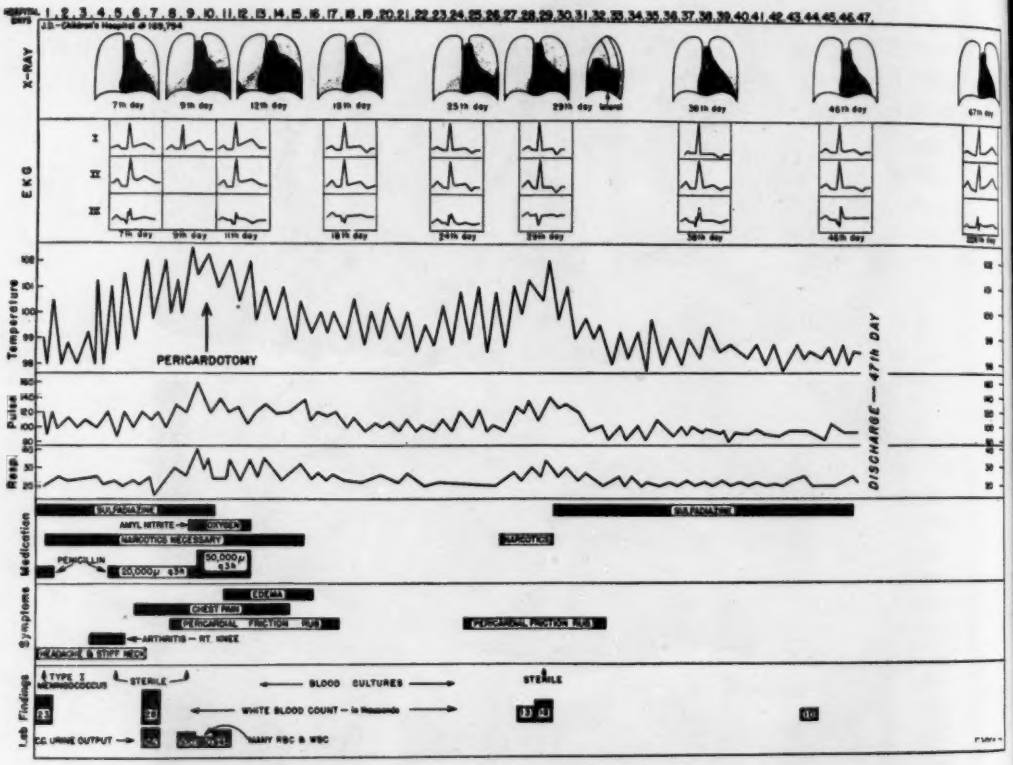

Fig. 2.—Chart showing patient's clinical course.

child began to complain of a pain in the left side of the chest and difficulty in breathing. Some component of the pain radiated down the left arm, left flank and abdomen. The temperature had reached 100.6 F., the pulse rate was 140, respirations were 25, and the blood pressure was unchanged. No rales were heard in the chest, and the heart sounds had not changed. Palpation revealed minimal left upper quadrant tenderness.

On the morning of the eighth day in the hospital, the pain in the chest had become worse, and the child cried constantly. The left side of the chest was dull to percussion in the anterior axillary line, but no rales or changes in breath sounds

were present. This dulness, it was felt, was probably due to an enlarging heart, since the heart sounds had become definitely poorer in quality. An electrocardiogram revealed some elevation of the RS-T takeoff in lead I, and was interpreted as indicating pericarditis. A roentgenogram of the chest showed a hazy density in the left lower lobe and in addition a minimal pleural effusion on the left side. The heart appeared somewhat enlarged. The temperature during the evening rose to 102, and a definite cardiac friction rub could be heard in the third left interspace along the sternum.

By the morning of the ninth day the friction rub was considerably louder, the apex sound more distant, and showers of fine, moist rales were heard at the base of the left lung. Because of fever and tachycardia, the dose of penicillin was increased to 50,000 units every three hours. The child continued to complain of almost constant pain, on the left side, part of which was associated with inspira-

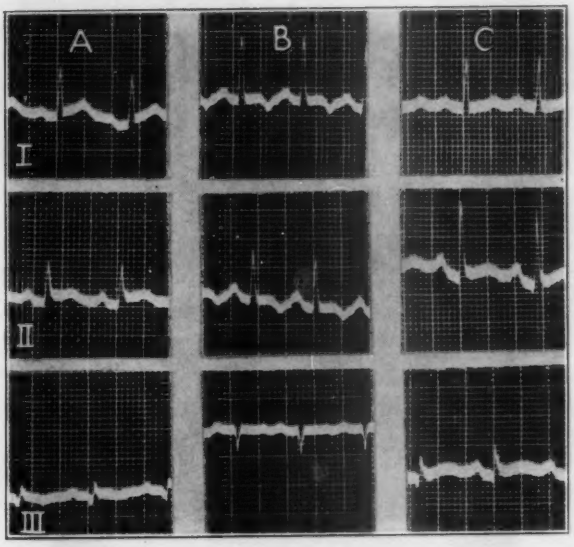

Fig. 3.—*A*, eleventh day of hospitalization. Note the high S-T take-off in leads I and II. *B*, twenty-ninth day of hospitalization. Note inversion of T waves in all leads. *C*, sixty-seven days after hospitalization. Note return to essentially normal configuration.

tion, and part of which was dull, constant and midsternal. Codeine sulfate administered by mouth had little effect on the constant dull ache, but gave almost complete relief from the intermittent sharp pains. Inhalations of amyl nitrite were tried for relief of the midsternal pain, with little benefit. During the night of the ninth day in the hospital difficulty in breathing was constant, and the midsternal pain unrelenting. The temperature rose to 102.6, and the pulse rate to 136. The whole left side of the chest was dull to percussion, and the heart was now markedly enlarged to the left. Rales were still present, and the pericardial friction rub even louder. A paradoxic type of pulse was noted for the first time.

The patient was seen in consultation by a cardiologist and by a cardiac surgeon. A pericardotomy was advised. A roentgenogram taken just before operation was begun revealed enlargement of the heart, much greater than that observed on the previous examination (fig. 4*A*). Under local anesthesia a pericardotomy was

performed.[1] Adhesions and fibrin were encountered under an edematous parietal pericardium, but no free fluid was noted either anteriorly or posteriorly when a catheter was passed around the heart. The epicaridum had several 1 to 2 cm., irregular, necrotic lesions on its surface, and these presumably involved the myocardium also. Because of the precarious state of the patient and fear of encountering a mycotic aneurysm, lysis of the adhesions and further exploration were not attempted.

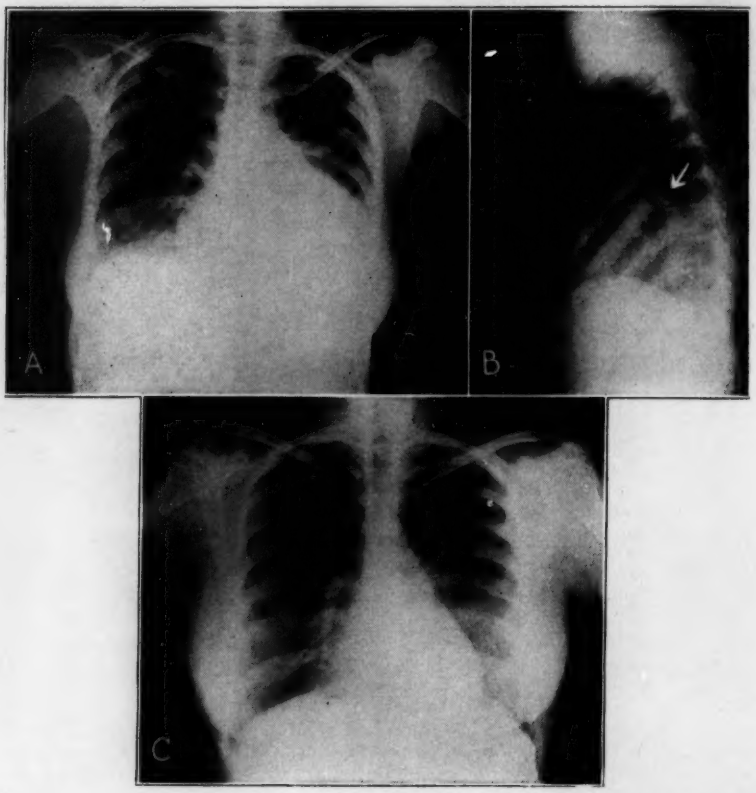

Fig. 4.—*A*, roentgenogram of chest obtained on ninth day of hospitalization, just preceding pericardotomy. *B*, roentgenogram obtained on twenty-ninth day of hospitalization. Note enlargement of heart posteriorly, possibly due to loculated effusion. *C*, roentgenogram seven months after onset of illness. Note relatively normal size and contour of heart.

Oxygen given postoperatively reduced tachypnea, but only morphine relieved the boring pain. For the first time there was evidence of cardiac failure, for rales were now present at the bases of both lungs and the veins in the neck were full and pulsating.

On the morning following operation, the tenth day in the hospital, pitting edema was present over the tibias, and the liver had enlarged one finger-breadth below the costal margin. The pulsus paradoxus was still present. On unrestricted

1. Operation was performed by Dr. Robert E. Gross.

fluid intake, the day's urine output fell abruptly to 640 cc., and specimens obtained were loaded with red cells. The intake of fluid and salt was restricted. An electrocardiogram showed an increased elevation of the S-T takeoff in all leads and notching of T_3, and the P-R interval was not pathologic (fig. 3*A*). Therapy with digitalis and theocalcin was considered, but within twenty-four hours the patient improved spontaneously, and the urine output increased.

Three days after operation the child's chest was clearer, and the edema had disappeared. A hacking cough productive of pink, mucoid sputum had been nagging and uncomfortable, but disappeared spontaneously and dramatically within forty-eight hours. Five days postoperatively the temperature fell to normal, and for the next week was no higher than 100. The signs in the chest slowly cleared, and the friction rub became difficult to hear.

For no apparent reason, eighteen days after operation the child began to have an elevation of temperature up to 101 every evening, accompanied by tachycardia frequently reaching 130 beats per minute. Blood cultures taken at this time were sterile. It was interesting that the cutaneous lesions, which had been necrotic two weeks before, were now healing, but had begun to slough devitalized tissue. It seemed most likely that similar myocardial and pericardial changes were occurring. With the rise in fever, substernal pain again became oppressive. The paradoxic pulse was once more noted, without evidence of heart failure, and rales were present in the region of Grocco's triangle. Therapy with oral administration of sulfadiazine was reinstituted. As suddenly as it began, the febrile episode subsided in five days. From then until the time of discharge, forty-seven days after entry, the patient's course was uneventful. One month after discharge there was a recurrence of precordial pain, severe enough to require morphine. It stopped spontaneously four days after its appearance without other symptoms or therapy.

Electrocardiograms were obtained two, four and six months after the onset of illness, and showed a slow return to a configuration that would be considered normal for the patient's age. Roentgenograms of the chest showed a gradual return of the heart to normal size, although some fulness of the cardiac waist was noted (figs. 3*C* and 4*C*). Fluoroscopy showed no abnormalities of heart dynamics.

The cutaneous lesions healed moderately well but left large scars (fig. 1*B*). Nine months after admission the youngster was carrying on full activity without complaint.

COMMENT

On admission, except for the normal temperature, this patient presented most of the symptoms of acute meningococcemia and meningococcic meningitis. History of intermittent rash for seven days was highly suggestive of repeated invasion of the blood stream without meningeal localization. The child's course in the hospital for the first three days was unusually satisfactory for one so severely ill. Generalized arthralgia noted on admission was similar to that seen in many severe infections, but the monoarticular arthritis present on the third day was distinct from the arthralgia and of the type frequently seen in meningococcic infection.

The gradually increasing pulse rate, present before pain or respiratory distress, apparently was a premonitory symptom of the child's cardiac complication (fig. 2). The occurrence of fever, tachycardia and poorly localized pain on the left side presented consider-

able diagnostic difficulty when first present. Numerous possibilities were considered. It was not until the appearance of a cardiac friction rub that the symptoms were related to cardiac complications.

As a possible cause of the cardiac signs, rheumatic carditis was considered. But more seriously discussed were the various cardiac complications of meningococcemia: cardiac abscess with or without rupture, acute toxic myocarditis, myocardial infarct and acute pericarditis. Numerous reports on meningococcemia[2] give the impression that the cardiac complications, though not frequent, when present are severe and usually fatal. The table gives some estimates of the frequency with which pericarditis and myocarditis have been reported in

Incidence of Cardiac Complications Associated with Meningococcemia

Author	No. of Cases	Age	Criteria for Diagnosis	Cases of Myocarditis	Cases of Pericarditis
Goldbloom[2h]	63	Army age	None given	1	0
McLean and Caffey[2c]	32	0-12 yr.	7 children died; autopsy on these	0	0
McLean and Caffey[2f]	136	0-5 yr.	None given	0	0
Borovsky[2d]	190	1-62 yr.	None given	0	0
Smithburn et al[2e]	144	All ages	None given	58	9
Neal et al[2g]	654	3 mo. to 60 yr.	No mention of autopsies	0	0
Herrick[2a]	280	Army age	Autopsy on 12 cases with pericarditis	0	12
Horwitz[2b]	471	All ages	None given	11	0

2. (*a*) Herrick, W. W.: Meningococcic Pericarditis with Report of Twelve Cases, M. Clin. North America **2**:411-426, 1918. (*b*) Horwitz, B. A.: Infeccion meningococia in Chile, Rev. med. de Chile **71**:125-136, 1943. (*c*) McLean, S., and Caffey, J.: Endemic Purpuric Meningococcus Bacteriemia in Early Life: Diagnostic Value of Smears from Purpuric Lesions, Am. J. Dis. Child. **42**:1053-1074 (Nov.) 1931. (*d*) Borovsky, M. P.: Clinical Study of Meningococcus Meningitis: Analysis of One Hundred and Ninety Cases Observed in a Period of Eighteen Months, Am. J. M. Sc. **179**:82-90, 1930. (*e*) Smithburn, G. C.; Kempf, A. F.; Zerfas, L. G., and Gilman, L. H.: Meningococcic Meningitis: Clinical Study of One Hundred and Forty-Four Epidemic Cases, J.A.M.A. **95**:776-780 (Sept. 13) 1930. (*f*) McLean, S., and Caffey, J. P.: Endemic Meningococcus Meningitis: Clinical Manifestations in Infancy and Early Childhood, Am. J. Dis. Child. **35**:357-387 (March) 1928. (*g*) Neal, J. B.; Jackson, H. W., and Applebaum, E.: Epidemic Meningitis: Study of More Than Six Hundred and Fifty Cases with Especial Reference to Sequelae, J.A.M.A. **87**:1992-1995 (Dec. 11) 1926, (*h*) Goldbloom, A.; Nickman, E., and Seidmon, E.: Meningococcic Infection in an Army Staging Area: Analysis of Sixty-Three Cases, Without Fatality from the Standpoint of Early Diagnosis and Treatment, Ann. Int. Med. **24**:589-605, 1946. (*i*) White, P. D.: Heart Disease, New York, The Macmillan Company, 1944, p. 644.

various large series of patients. At the Boston Children's Hospital a review of 5,000 autopsies revealed only 1 case of questionable cardiac complications associated with meningococcic infection.[3] Apparently in the past these conditions have been but poorly differentiated, and occasionally when a clinical diagnosis of myocarditis has been made the autopsy material has not confirmed it. Similarly the diagnosis of pericarditis frequently has not been substantiated by laboratory findings.

The literature contains no reference to myocardial infarct associated with meningococcemia, and with this in mind this diagnosis was not further pursued.

Saphir in 1936[4] reported 2 cases of myocardial abscess associated with meningococcemia. Except for this report, no other clinical records of cases having this complication have been found except as associated with meningococcic endocarditis.[5] Endocarditis without a murmur and sterile blood cultures is unlikely, and according to a recent report[6] meningococcic endocarditis without a murmur is unknown. Therefore this possibility was not further considered.

In the same report in 1936 in which Saphir[4] reported myocardial abscesses he also reviewed the early literature on meningococcic myocarditis. His own 2 patients showed microscopic evidence of diffuse involvement of the muscle fibers of the heart in areas free of abscess formation. Of the early cases reviewed, few were confirmed by autopsy, and none of them had electrocardiographic or roentgen evidence for the diagnosis of myocarditis. It is interesting, however, that Herrick in 1918[7] made the statement that there had been reported no cases of "true meningococcal myocarditis" up to that time. It is conceivable that the flabby hearts described on gross examination in the early reports did not necessarily show myocarditis specifically due to the meningococcus, but were like those which occasionally have been found in other severe infections,[8] particularly pneumonia,[9] typhoid

3. Farber, S.: Personal communication to the authors.

4. Saphir, O.: Meningococcus Myocarditis, Am. J. Path. **12**:677-688, 1936.

5. (*a*) Whillans, M. G.: Meningococcus Endocarditis and Myocarditis: Report of Case witrh Unusual Lesions on the Arterial Tree, Am. J. Path. **16**:365-374, 1940. (*b*) Hartwell, R. M.: Meningococcic Endocarditis and Myocarditis, Am. J. Dis. Child. **58**:823-829 (Oct.) 1939.

6. Firestone, G. M.: Meningococcus Endocarditis, Am. J. M. Sc. **211**:556-565, 1946.

7. Herrick, W. W.: Meningococcus Infections, in Nelson Loose-Leaf Living Medicine, New York, Thos. Nelson & Sons, 1927, vol. 2, p. 45.

8. Saphir, O.: Myocarditis: General Review with Analysis of Two Hundred Forty Cases, Arch. Path. **33**:88-137 (Jan.) 1942.

9. Master, A. M., and Romanoff, A.: Electrocardiogram Changes in Pneumonia, Proc. Soc. Exper. Biol. & Med. **28**:266-267, 1930.

fever,[10] and influenza.[11] Between 1936 and 1945, two other reports of meningococcic myocarditis appeared.[12] These cases apparently are better substantiated, for when the diagnosis was made it was confirmed by electrocardiographic and roentgen evidence as well as autopsy material. The diagnosis of myocarditis appears to be less well proved in the case reported by Rappaport and Zuckerbrod[12a] although pericarditis seems definite.

Acute cardiac dilation associated with pericarditis and heart failure without specific electrocardiographic changes can also, however, be evidence of myocarditis. When present in a disease such as influenza, the course may be rapidly fatal.[11] This aspect of myocarditis certainly was present in our patient.

On reviewing the incidence of meningococcic pericarditis, it is apparent that this condition is not common. Herrick reported 12 cases in 1918[2a] and in several larger series of cases reviewed from 1918 to 1946 a varying incidence has been reported (table). None of the reported series with the exception of that of Herrick presents any evidence from which an adequate statement of incidence can be obtained. Few give criteria for the diagnosis, and none publishes autopsy protocols except Herrick. The recent well authenticated instances of meningococcic pericarditis[13] are reported singly rather than as part of a series, and thus can serve to give no conception of the incidence of the complication. At best one can only state that meningococcic pericarditis is unreported in children and rare in adults.

Certainly this diagnosis must be entertained at any time a friction rub is present, but the problem of deciding whether the pericarditis is the sole cardiac disease or secondary to infarct, abscess, rheumatic

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10. Brow, G. R.: The Heart in Typhoid Fever, Canad. M. A. J. **20**:606-609, 1929.

11. Finland, M.; Parker, F., Jr.; Barns, M. W., and Jolliffe, L. S.: Acute Myocarditis in Influenza A Infection: Two Cases of Non-Bacterial Myocarditis with Isolation of Virus from the Lungs, Am. J. M. Sc. **209**:455-468, 1945.

12. (*a*) Rappaport, J. N., and Zuckerbrod, M.: Recovery from Fulminating Meningococcic Infection with Myocarditis, Proved by Electrocardiography, J. Lab. & Clin. Med. **30**:307-316, 1945. (*b*) Holman, D. V., and Angevine, D. M.: Meningococcus Myocarditis: Report of Two Cases with Anatomical and Clinical Characteristics, Am. J. M. Sc. **211**:129-137, 1946.

13. (*a*) Rappaport and Zuckerbrod.[12a] (*b*) Trace, I. M., and Bercovitz, C.: Meningococcic Purulent Pericarditis, Complicating Epidemic Cerebrospinal Meningitis: Recovery After Treatment with Intrapericardial Injections of Antimeningococcus Serum, J.A.M.A. **97**:246-247 (July 25) 1931. (*c*) Urschel, D. L.; Bondy, P. K., and Salley, S. M.: Acute Pericarditis: Graphic Correlation of X-Ray, Clinical and Electrocardiogram Findings, New England J. Med. **233**:399-407, 1945.

fever or azotemia is frequently difficult. White[21] and others[14] agree that acute pericarditis is always accompanied by some degree of myocarditis.

In a comprehensive review by Urschel and others in 1945,[13c] characteristic electrocardiographic changes have been enumerated. The elevation of the RS-T takeoff is present only in acute pericarditis associated with a rapidly developing effusion. This is probably secondary to acute anoxia of the peripheral myocardium from pressure of accumulated fluid.[14] Inversion of the T wave in any or all limb leads appears between the tenth and eighteenth days in acute pericarditis, and at any later time in chronic pericarditis. The late inversion of the T wave is evidence of necrosis in the same layer of myocardium that early in the disease was anoxic. This layer evidently heals with fibrosis, but in electrocardiograms obtained between two and six months after the acute episode, there is usually no evident abnormality.

The episode of edema, basilar rales, tenderness in the right upper quadrant and dyspnea that occurred five days after the appearance of pericarditis can be interpreted either as evidence of myocardial failure or as severe cardiac tamponade. The findings at pericardotomy were interesting, and the fact that no pus was present seems explained by the intensive chemotherapy. Certainly most of Herrick's patients who came to autopsy had considerably more fibrin than fluid in the pericardial sac. The combination of bilateral basilar rales and enlarged liver, edema, rapidly dilating heart without evidence of much pericardial fluid on visual examination and electrocardiographic changes would seem to make the diagnosis of acute myocarditis with dilatation and secondary failure inescapable. Thus this youngster presumably suffered from both myocarditis and pericarditis. It seems doubtful that tamponade played any part in her symptomatology.

The cause of the febrile episode with tachycardia and leukocytosis on the twenty-first day could not be adequately explained. Blood cultures taken at that time were sterile. It is possible that the abnormalities represented a delayed response to sulfonamide idiosyncrasy. The transient hematuria on the tenth day conveivably belongs in this category also. Whether there were local lesions in the kidneys similar to those on the skin remains unknown. Certainly in this child, as has been so frequently demonstrated in numerous other patients with meningococcemia, we have overwhelming evidence of involvement of numerous organs and tissues with thrombotic lesions in capillaries.

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14. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis: Evolution, Causes, and Diagnostic Significance of Patterns in Limb and Chest Leads; Study of Fifty-Seven Cases, Arch. Int. Med. **61**:381-400 (March) 1938.

CONCLUSIONS AND SUMMARY

Presented is the case of a 13 year old white girl who was ill with meningococcemia and meningococcic meningitis, and in whom there developed evidence of pericarditis, cardiac dilatation, heart failure, peripheral edema, electrocardiographic changes and finally severe necrotic cutaneous lesions. The acute cardiac dilatation was felt to be due to myocarditis and pericarditis, and this was substantiated by the findings at pericardotomy.

Chemotherapy was undoubtedly responsible for the recovery of this child. This therapy also probably explains why serum and not pus was found in the pericardial sac. It is suggested that the lesions seen on the pericardium at operation followed a course similar to that of the cutaneous lesions. That cardiac complications have been rarely reported in meningococcic disease can possibly be explained by the fact that previous to chemotherapy patients with such overwhelming sepsis died before development of this complication.

VALUE OF ROUTINE ROENTGENOGRAMS OF THE WRIST IN A PEDIATRIC SERVICE

M. G. PETERMAN, M.D.
W. B. FREY, M.D.
AND
J. D. KASTER, M.D.
MILWAUKEE

ROENTGENOGRAMS of the wrists of children taken casually during the past few years, in private practice, have revealed such a large number of unsuspected conditions that the procedure has now been established as routine. There are a number of pathologic entities in children the existence of which can frequently be readily detected or suggested by roentgenograms of the wrists. Of these, some may be discovered at their incipience, while in others, which are in advanced or clinically obscure stages, focus may be brought for the first time on the underlying cause by the use of this procedure. The distal ends of the ulna and radius are the optimal sites for the demonstration of the earliest rachitic lesions by roentgenogram. All of the metaphysial changes of scurvy appear earliest and are most marked at the sites of most rapid growth and most active endochondral bone formation, among which are the distal ends of the radiuses and ulnas. Marked central rarefaction with intensification of the margin in the ossification center is one of the most characteristic roentgen findings in scurvy.[1] Lead intoxication, from prolonged ingestion or inhalation by infants and children, may be suggested by the heavy transverse lines which develop in the ends of the shafts of long bones. Visualization of these heavy metal lines by roentgenograms of the distal ends of the radiuses and ulnas is possible. In his private practice one of us (M. G. P.) has observed 2 cases of lead intoxication within the past two years whose underlying pathologic process was first suggested by roentgenograms of the wrist. One of these patients had previously been studied at a medical clinic without intimation of the diagnosis. In infantile syphilis the juxta-epiphysial segments of the shaft are usually the earliest sites of involvement of bone. Although none of the syphilitic skeletal lesions is conclusively diagnostic in itself, such findings may

1. Caffey, J.: Pediatric X-Ray Diagnosis, Chicago, The Year Book Publishers, Inc., 1945, p. 703.

suggest the presence of active syphilis even before the serologic reaction becomes positive or when clinical evidence is lacking, or augment other evidence favoring its presence.

Concerning the rate of bone maturation and the appearance of the centers of ossification in the wrist there have been wide variations, as may be noted in the investigations of Scammon,[2] Flory,[3] Clark,[4] Pryor,[5] Pyle and Sontag,[6] Hodges,[7] Francis,[8] Flecker,[9] and others. Leonard[10] has summarized the studies of ossification centers in the wrist by these authors and has proposed his "ossification index" as a standard for practical use. That a delay in the appearance of ossification centers occurs almost always in long-standing, untreated hypothyroidism in children has been known for some time. Numerous authors, Clark,[4] Dutton,[11] Kennedy[12] and others, have noted that study of the ossification centers by roentgenogram is a valuable source of information in the diagnosis of hypothyroidism in children. Dutton has also observed allergic children in whom there was an accompanying retardation of bone age. We have observed borderline cases of hypothyroidism in children in whom retardation of bone maturation first cast light on the underlying condition. Use of basal metabolism studies is of little clinical value in children.[13] Wilkins, Fleischmann,

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2. Scammon, R. E., and Morris, H.: Morris' Human Anatomy, ed. 10, Philadelphia, The Blakiston Company, 1942.

3. Flory, C. D.: Osseous Development in the Hand as an Index of Skeletal Development, Monograph of the Society for Research in Child Development, Washington, D. C., National Research Council, 1936, vol. 1, pt. 3, table 5, p. 35.

4. Clark, D. M.: Practical Value of Roentgenography of Epiphyses in Diagnosis of Pre-Adult Endorcine Disorders, Am J. Roentgenol. **35**:752-771, 1936.

5. Pryor, J. W.: Roentgenographic Investigation of Time Element in Ossification in Epiphyses and Short Bones of Extremities, Am. J. Roentgenol. **29**:798-804, 1933.

6. Pyle, I., and Sontag, L. W.: Variability in Onset of Ossification in Epiphyses and Short Bones of the Extremities, Am. J. Roentgenol. **49**:795-798, 1943.

7. Hodges, P. C.: Epiphyseal Chart, Am. J. Roentgenol. **30**:809-810, 1933.

8. Francis, C. C.: Factors Influencing Appearance of Centers of Ossification During Early Childhood, Am. J. Dis. Child. **57**:817-830 (April) 1939.

9. Flecker, H.: Time of Appearance and Fusion of Ossification Centers as Observed by Roentgenographic Methods, Am. J. Roentgenol. **47**:97-159, 1942.

10. Leonard, D. W.: Early Recognition of Endocrine Disorders in Childhood by Roentgenograms of the Wrist to Determine the "Ossification Index," Am. J. Roentgenol. **53**:55-61, 1945.

11. Dutton, L. O.: Bone Age Studies in Children to Establish Diagnosis of Hypothyroidism, Ann. Allergy **4**:461-462, 1946.

12. Kennedy, R. L., in Brennemann, J.: Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1946, vol. 1, chap. 38, p. 29.

13. Wolman, I. J.: Basal Metabolism in Childhood: Current Progress, Am. J. M. Sc. **211**:733-742, 1946.

and Block[14] found in studying basal metabolic rates in children with hypothyroidism that in only 1 out of every 4 children satisfactory determinations were obtained. Even when the performance was satisfactory the selection of a proper standard for comparison was difficult. Wilkins and Fleischmann[15] found a low excretion of creatine to be of limited diagnostic value. The investigations of these same authors revealed the response of osseous development to thyroid to be a good index as to whether the child was receiving adequate dosage. In some of the cases of adrenal cortical disease with increased 17 ketosteroids studied by Kennedy[16] precocious skeletal development occurred; in other cases of the same condition it was found to be normal. In the present series 1 case of pubertas precox exhibited a markedly advanced bone age. In a study of endocrine dwarfs made by Engelbach and Schaefer[17] 5 of the 7 patients exhibited delay in osseous development. Roentgenograms of the wrist have been used as an aid in differentiating cretinism from mongoloidism. Retardation of the secondary ossification centers and epiphysial dysgenesis in the former condition are frequently pronounced. The cuboidal formation of the middle phalanx of the little finger may be noted in mongoloid persons by roentgen examination. In our series 2 cases exhibited this defect. Other conditions in which there is a delay in ossification are chronic renal disease, glycogen disease and many other chronic metabolic diseases, as well as deficiency in the intake of vitamin D and minerals.[18] In the present series delayed ossification was noted to be associated with mental retardation and congenital heart disease, cerebral birth injury, chronic fibrocystic disease of the pancreas, cerebral dysgenesis with hypothyroidism and allergy.

PRESENT INVESTIGATION

With the foregoing evidence in mind it was deemed advisable to make an investigation of roentgenograms of the wrists of children to determine whether it behooves the physician, both in the hospital pediatric service and in private practice, to make a routine roentgen

14. Wilkins, L.; Fleischmann, W., and Block W.: Studies on Hypothyroidism in Childhood: The Basal Metabolic Rate, Serum Cholesterol and Urinary Creatine Before Treatment, J. Clin. Endocrinol. **1**:3-13, 1941.

15. Wilkins, L., and Fleischmann, W.: Diagnosis of Hypothyroidism in Childhood, J. A. M. A. **116**:2459-2465 (May 31) 1941.

16. Kennedy, R. L.: Precocious Skeletal Development, J. A. M. A. **127**:580-581 (March 10) 1945.

17. Engelbach, W., and Schaefer, R. L.: Endocrine Dwarfism, J. A. M. A. **103**:464-468 (Aug. 18) 1934.

18. Mitchell, A. G., and Nelson, W. E.: Textbook of Pediatrics, Philadelphia, W. B. Saunders Company, 1945, pp. 1124-1125.

Fig. 1.—A. S., 10 month old boy with active rickets.

Fig. 2.—P. F., 3 year old boy with clinical evidence of hypothyroidism and a bone age of 2 years.

examination of the wrists of all children under observation. To our knowledge no similar studies for this purpose have been carried out. Leonard[10] has adopted routine roentgenograms of the hand for investigation of the "ossification index." Our present work would indicate that this simple procedure when carried out routinely affords the physician an inexpensive and valuable aid in clinical diagnosis. Few areas in the child's body as small as the wrist, which can be easily visualized, reveal such a wealth of useful information.

During the past twelve months at the Milwaukee County Hospital Pediatric Service routine roentgenograms were taken of infants

Fig. 3.—L. G., a 7 month old boy with clinical signs of rickets confirmed by roentgen examination.

and children of all ages up to 14 years. All patients in this hospital are indigent. During the past year a similar study was made in the private practice of one of us (M. G. P.) on infants and children ranging in age from 6 months to 16 years. The total number of roentgenograms of the wrist in the hospital series was 333, while the total number in the private series was 351. It was decided that both of these groups be incorporated and be reported on at the same time. As may be noted in table 1, of the total number of investigations made in the hospital series, 34 or 10 per cent revealed abnormal findings

in roentgenograms of the wrist. Of the entire hospital series, 10 exhibited evidence of rickets (tables 1 and 3). The ages range from 3½ to 19 months. There were 2 girls and 8 boys in this group; 2 were Negro and 8 were white. The history revealed that all but 2 had received cod liver oil since early infancy. Craniotabes was the only significant rachitic characteristic in 4 of the cases. Two cases exhibited

TABLE 1.—*Number of Abnormal Findings in Routine Roentgenograms of Wrists in Children at Milwaukee County Hospital*

Total Number of Roentgenograms in Series	333
	Number of Cases
Delay in "ossification index" (Leonard)	14
Hypothyroidism	6
Cause undetermined	6
Multiple congenital anomalies and mental deficiency	1
Epidermolysis bullosa hereditaria	1
Rickets	10
Scurvy	2
Congenital syphilis	2
Osteochondroma, distal one third of radius	1
Sclerosis at metaphysial ends of radiuses and ulnas with areas of decreased density proximal to the sclerosis	1
Periostitis of entire ulna, cystlike formations at base of first and third metacarpal bones with a fracture of the lateral cortical surface	1
Cystic changes, medullary cavities of metacarpal bones; some eburnation at distal ends of radius and ulna with a growth-arrest line in metaphysial portion of radius, suggestive of Cooley's anemia	1
Osteitis, left ulna	1
Periostitis involving shafts of both ulnas and radiuses, soft tissue calcification adjacent to lateral aspect of first metacarpal shaft, rt. side	1
Total	34
Per cent abnormal	10.21

TABLE 2.—*Number of Abnormal Findings in Routine Roentgenograms of Wrists in Children (Private Practice of M. G. Peterman)*

Total Number of Roentgenograms in series	351
	Number of Cases
Delay in "ossification index" (Leonard)	24
Hypothyroidism	14
Cerebral birth injury residue and convulsions	3
Cause undetermined	3
Fibrocystic disease of pancreas	1
Pituitary dwarfism	1
Mental retardation	1
Cerebral dysgenesis with hypothyroidism	1
Rickets	6
Mongoloidism (cuboid middle phalanx little finger)	2
Lead intoxication (lead lines)	1
Pubertas precox with advanced bone age	1
Chondrodystrophy	1
Total	35
Per cent abnormal	9.97

bossing of the frontal and parietal bones in addition to the craniotabes, and in 1 of the latter, flattening of the bony thorax, rachitic rosary and slight Harrison's groove were also found. Three cases revealed no rachitic stigmas. The remaining case showed a suggestive Harrison's groove. Areas of softening in the parietal and occipital regions have been noted in several nonrachitic patients with no other

TABLE 3.—*Summary of Data on Children with Rickets and Positive Roentgen Evidence in the Wrists*

Case	Age	Race	Sex	History of Cod Liver Oil Intake	Rachitic Stigma	Serum Calcium Mg./100 Cc.	Serum Phosphorus Mg./100 Cc.	Blood Phosphatase Bodansky Units	Anemia	Positive Roentgen Evidence of Rickets
(1) G. V.	4 mo.	W	F	No intake	Present	9.4	4.35	No report	Marked	Present
(2) L. G.	7 mo.	W	M	Received	Present	11.0	3.57	4.0	Mild	Present
(3) J. R.	19 mo.	W	M	Received	Suggestive Harr. groove	10.0	No report	11.8	None	Present
(4) A. S.	10 mo.	W	M	No intake	Present	13.3	3.43	9.3	Moderate	Present
(5) J. B.	4 mo.	W	M	Received	Not report.	N. R.	N. R.	28.9	Marked	Present
(6) I. L.	3½ mo.	N	F	Received	Present	N. R.	N. R.	16.8	Mild	Present
(7) W. W.	3½ mo.	N	M	Received	Present	N. R.	N. R.	22.3	None	Present
(8) K. W.	5½ mo.	W	M	Received	Present	10.9	3.5	41.1	None	Present
(9) I. D.	5 mo.	W	M	Received	None (hydroceph)	Not done	Not done	Not done	Mild	Present
*(10) H. T.	6 mo.	W	M	Received	None	11.0	3.6	Not Reported	Moderate	Present

*Also delay in "ossification index" 6 mo.—00-0000000.

abnormal clinical or laboratory findings or roentgen evidence of rickets.

Of six serum calcium determinations all were normal except that in case 4 which was 13.3 mg. per hundred cubic centimeters. Of five serum phosphorus determinations four ranged between 3.43 and 3.6 mg. per hundred cubic centimeters of serum; one was 4.35 mg. Four of the blood phosphatase determinations were above 15 Bodansky

Fig. 4.—B. S., a 2½ month old girl with clinical and roentgenologic evidence of congenital syphilis.

units, the highest being 41.1. Three phosphatase determinations were 4.0, 9.3 and 11.8 Bodansky units.

Mild to marked anemia was noted in 7 of the 10 cases. All patients of this series had roentgenologic evidence of rickets consisting of cupping and flaring of the distal metaphyses of the radiuses and ulnas. Some cases showed zones of eburnation suggesting arrest of growth. Case 10, in addition to the roentgenologic evidence of rickets, exhib-

TABLE 4.—*Summary of Data on Children with Hypothyroidism and Delayed "Ossification Index"*

Case		Age	Sex	"Ossification Index" (Leonard)	Serum Cholesterol Mg./100 Cc.	Urine Creatine Mg./Kg. 24hr.	Basal Temp., Pulse	Signs and Symptoms	Therapeutic Response to Thyroid Extract
(11)	J. R.	12 mo.	F	1-00-0000000	227.0	—	Low, slow	Mental torpor, dull facies, lassitude, unable to sit or stand, anemia	Good
(12)	L. M.	7 yr.	M	7-67-2400000	181.1	—	Low, slow	Dull mentally, pallor, six year molars not erupted, anemia	Observed as outpatient
(13)	P. F.	3 yr.	M	3-67-0000000	264.0	—	Low, slow	Dull facies, unable to stand or talk; hair coarse and dry; marked lassitude; rocking habit spasm	Good
(14)	E. N.	3 yr.	M	3-67-0000000	136.0	3.2	Low	Underdeveloped, mentally dull, retarded eruption teeth, retarded speaking ability	Fair
(15)	L. M.	6½ yr.	M	6-67-2400000	157.6	2.9	Low, normal	Hypothyroid facies, eyes wide apart, small, underdeveloped, mentally dull, hyperactive	Fair
(16)	J. M.	6 yr.	M	6-67-2450000	294	10.3	Low	Normal intelligence, no anemia, small stature, underweight.	Observed as outpatient

ited a delay in ossification. The "ossification index" was 6 month-00-0000000. This could be compatible with rickets.

Table 4 is concerned with 6 cases of hypothyroidism. There were 5 boys and 1 girl, with an age range of 1 to 7 years. In order to establish the diagnosis of hypothyroidism definite clinical findings, roentgenologic evidence of osseous retardation, laboratory determinations and a satisfactory response to thyroid extract were required. In general all 6 patients showed physical and mental retardation, anemia, low basal temperature, a slow pulse rate and a delay in appearance of the centers of ossification. In 2 patients the serum cholesterol level was 264 and 294 mg. per hundred cubic centimeters. In the remaining 4 it ranged from 136 to 227 mg. It may be noted that the patient

Fig. 5.—J. R., a 14 month old girl with clinical evidence of hypothyroidism. No bone centers were shown on roentgenograms.

in case 11, who had the most severe hypothyroidism and showed a remarkable response to therapy, had a serum cholesterol level of only 227 mg. per hundred cubic centimeters. As has been shown by Wilkins and Fleischmann,[15] patients with severe hypothyroidism have been found to have serum cholesterol levels as low as 150 mg. per hundred cubic centimeters. A low cholesterol level does not exclude hypothyroidism. As has been stated previously, a low excretion of creatine is of limited diagnostic value. In 3 patients of this group the range of the urinary creatine level was from 2.9 to 10.3 mg. per kilogram of body weight per twenty-four hours. A good response to thyroid therapy was observed in patients 11 and 13, and a fair response in

patients 14 and 15. Patients 12 and 16 are being observed on an outpatient status; however, it was felt that the findings in these cases were sufficient to substantiate the diagnosis of hypothyroidism. There was a total of 14 patients with a delay in the "ossification index." A group of 8 patients was studied in whom there was a delay in the bone ossification and in whom further investigation did not yield sufficient findings to warrant a diagnosis of hypothyroidism. The age range in this group was 8 months to 8 years. All were boys. Four of these patients were admitted for an infection of the upper respiratory tract and for the fifth the final diagnosis was psoriasis. One patient was observed in whom a delayed bone age was found accompanying multiple congenital anomalies, mental retardation and dwarfism. Another patient who entered the hospital because of epidermolysis bullosa hereditaria also was found to have a retarded bone age without evidence of hypothyroidism. The last patient in this group entered the hospital for observation of a foreign body.

Studies of the serum cholesterol were made on 5 of the 8 patients. It ranged from 135 to 225 mg. per hundred cubic centimeters. Except in 1 case a diagnosis of hypothyroidism could not be established, nor could any of the other known causes for delayed maturation of bone be determined. At the time of writing this paper patient 17 is still under study. Some evidence points to hypothyroidism; however, he was placed in this group until a more positive diagnosis can be made. According to the standards of Leonard,[19] if there is a delay in the "ossification index" it can be accepted as unmistakably abnormal. It is no doubt true that some borderline cases of delayed maturation of bone will be overlooked by using the Leonard "ossification index" for interpretation; nevertheless, it was desired in our investigation to deal only with definitely abnormal cases. If the standards of Todd had been used, the number of patients exhibiting delay in bone maturation would be greater.

Patient 17 of this group had an "ossification index" as follows: 1-60-0000000; patient 18, 8-67-2056778; patient 19, 5-67-2400000; patient 20, 8 mo.-60-0000000; patient 21, R. 2-67-0000000, L. 2-67-2000000; patient 22, 4-67-2000000; patient 23, 5-67-2400000; patient 24, 4-67-2000000.

In 2 patients with roentgenologic evidence of early scurvy, one, a 3½ month old girl, had a dietary intolerance to orange juice and had received none after several offerings. No synthetic ascorbic acid was given to the patient. The blood ascorbic acid level was 0.58 mg. per hundred cubic centimeters (Farmer and Abt). Clinically the only

19. Leonard, D. W.: Revised "Ossification Index" for the Detection of Endocrine Disorders in Childhood, Am. J. Roentgenol. **56**:716-721, 1946.

TABLE 5.—*Summary of Data on Children with "Delayed Ossification Index" Cause Undetermined*

Case	Age	Sex	"Ossification Index" (Leonard)	Serum Cholesterol Mg./100 Cc.	Urine Creatine Mg./Kg. 24 Hr.	Reason for Admission to Hospital	Signs and Symptoms
(17) N. G.	1 yr.	M	1-60-0000000	135.0	2.2	Upper respiratory infection, conjunctivitis	Normal boy, active, well developed
(18) D. M.	8 yr.	M	8-67-2056778	225.0	—	Psoriatic lesions	Normal mental development
(19) D. W.	5 yr.	M	5-67-2400000	156.2	—	Cervical adenitis, impetigo	Low basal temp., underdeveloped, mentally alert (still under study)
(20) C. K.	8 mo.	M	8 mo.—60-0000000	—	—	Upper respiratory infection, bronchitis, excoriated buttocks	Well developed, well nourished, happy infant
(21) J. B.	2 1/3 yr.	M	L. 2-67-2000000 R. 2-67-0000000	193.8	—	Upper respiratory infection, tonsilitis	No symptoms or signs of hypothyroidism
(22) K. C.	4 yr.	M	4-67-2000000	—	—	Upper respiratory infection, tonsilitis, rt. otitis media	Cong. heart disease, polydactylism, syndactylism, mental retard., bilateral cervical ribs
(23) S. G.	5 yr.	M	5-67-2400000	195.0	17.5	Epidermolysis bullosa hered.	Small stature, normal intelligence, normal activity, no anemia
(24) L. D.	4 yr.	M	4-67-2000000	—	—	Observation for possible foreign body	Slight mental retard., hair coarse and dry,low basal temp., development normal

TABLE 6.—*Summary of Data on Children with Scurvy, Syphilis, Osteochondromatosis and Inflammatory Changes*

Case	Age	Sex	Race	Clinical Findings	Laboratory Findings	Routine Roentgenograms of Wrists
(25) K. W.	3½ mo.	F	W	Fever, dyspnea, irritability, coryza, cyanosis; no orange juice given	Ascorbic acid 0.58 mg./100 cc.	Pelkan's sign, distal ulnar metaphyses, early scurvy
(26) R. D.	3½ mo.	M	W	Marasmus, pallor, dehydration, diarrhea; no orange juice	Vitamin C level not reported	Thinning of cortices of ulnas and radiuses with a haziness of medullary canal, early scurvy
(27) I. P.	10 days	M	W	Cord Wassermann test positive; mother syphilitic, not treated in pregnancy	Positive Wassermann test	Distal ends of ulnas and radiuses reveal zones of epiphysitis and osteochondritis
(28) B. S.	2½ mo.	F	N	Fracture deformities of both wrists	Wassermann test positive in all dilutions, spinal fluid negative	Extensive osteolytic destruction, principally confined to metaphysial portions of radiuses and ulnas; osteitis, periostitis also seen of metacarpal bones; other long bones also revealed periostitis, osteitis and perichondritis
(29) D. P.	12 yr.	M	W	From Children's Home, possible rheumatic fever		Small osteochondroma, distal 1/3 of rt. radius on routine roentgenogram of wrists
(30) K. H.	2 yr.	M	W	Admitted for mental and physical retard	Kline test negative, Mantoux test neg., Ca. 13.3 mg./100 cc. P. 3.63 mg./100 cc.	Periostitis in ulnas in entire shaft of medullary canal; small cyst with a break in lateral cortical surface; base third metacarpal showed two small cystlike areas, cyst also in base of first metacarpal
(31) C. W.	10 days	M	W	Admitted for facial dermatitis	Kline test negative	Sclerosis at the metaphysial ends of radiuses and ulnas with areas of decreased density proximal to the sclerosis
(32) J. L.	2 mo.	M	W	Admitted for bronchopneumonia	Urine neg., Mantoux, Kline tests neg.	Periostitis involving shafts of both ulnas and radiuses, soft tissue calcification adjacent to lateral aspect of first metacarpal shaft, rt. side
(33) C. W.	3 mo.	M	N	Generalized diffuse papular rash, 1 month duration	Kline test neg. on two occasions: diagnosis of atopic dermatitis	Small area of destruction at left distal ulnar metaphysis; other long bones normal
(34) A. S.	1 yr.	M	N	Upper respiratory infection	Kline test neg., complete blood count normal, chest and skull roentgenograms negative	Medullary cavities of the metacarpal bones showed cystic changes, eburnation of radiuses and ulnas, growth arrest line in radial metaphysis (suggestive of Cooley's anemia)

evidence pointing to scurvy was marked irritability. No hemorrhagic tendencies were noted. The second patient exhibiting scurvy was a 3½ month old white boy who came from an indigent home and entered the hospital with a diagnosis of severe malnutrition. The birth weight was 6 pounds 6 ounces (2,891.6 Gm.); admission weight was 7 pounds (3,175.1 Gm.). There was evidence of severe dehydration, marked pallor, diarrhea and malnutrition. Laboratory facilities were not available on admission and because of his poor condition ascorbic acid along with other therapeutic measures was administered immediately.

In case 25 the roentgenologic findings revealed a Pelkan's sign[20] in the distal ulnar metaphyses. Thinning of the cortices of the ulnas and radiuses with a haziness of the medullary canals was noted in case 26 (table 6).

Two patients observed had evidence of syphilis on roentgen visualization which consisted of zones of epiphysitis and osteochondritis in the distal ends of the ulnas and radiuses, and 1 of these patients showed bilateral transverse fractures of the radiuses and ulnas. A study of the other long bones also revealed marked syphilitic findings. The first infant was a 10 day old white boy whose mother was known to have syphilis of long standing and was untreated during pregnancy. The reaction to the Wassermann test of the cord was positive and a diagnosis of infantile syphilis was made. The second was a 2½ month old Negro girl who had evidence of marked syphilitic osseous involvement in all long bones.

A routine roentgenogram of 1 patient revealed a small osteochondroma in the distal one third of the right radius. Another similar tumor was found in the upper one third of the right humerus. No external evidence of multiple osteochondromatosis was noted. The patient was a 12 year old white boy who entered the hospital for a study of possible rheumatic fever.

One patient, a white boy 2 years and 8 months of age, whose presenting picture was one of physical and mental retardation and diarrhea was found to have periostitis in the entire shaft of the ulna. The medullary canal showed a small cyst with a break in the lateral cortical surface. The base of the third metacarpal bone revealed two small cystlike areas. The base of the first metacarpal bone revealed an irregular trabecular pattern with early cyst formation. The roentgenologic impression was chronic inflammatory involvement. These findings were not present on films taken six weeks later.

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20. Spurring of the diaphysial extremity. This is not a true spurring but is simply a result of weakness of the translucent osteoporotic area and slight displacement of the dense area.

The roentgen findings in the wrists of patient 31, a 10 day old white girl, were sclerosis at the metaphysial ends of the radiuses and ulnas, with areas of decreased density proximal to the sclerosis. This infant was hospitalized because of dermatitis of the face. The reaction to the Kline test of the blood was negative.

Case 32 was that of a 2 month old white boy, admitted to the hospital because of pneumonia, from which he recovered uneventfully. Roentgenograms of the wrists showed periostitis involving the shafts of both ulnas and radiuses; there was calcification of the soft tissue adjacent to the lateral aspect of the first right metacarpal bone. The Kline and Wassermann tests of the blood gave negative results.

Case 33 was that of a 3 month old Negro boy who entered the hospital for treatment of atopic dermatitis. The reaction to the Kline test was negative on two occasions. Routine roentgenograms of the wrists revealed a small area of destruction at the left distal ulnar metaphysis. Roentgen impression was osteitis of the left ulna. Other long bones were normal on the roentgenograms.

The remaining patient (case 34), a 1 year old Negro boy, was admitted to the hospital because of an infection of the upper respiratory tract. Routine roentgenograms of the wrists showed suggestive cystic changes in the medullary cavities of the metacarpal bones and eburnation of the distal ends of the radius and ulna with a growth-arrest line in the metaphysial portion of the radius. The roentgenologic impression was that the findings were suggestive of Cooley's anemia. There were no abnormal findings in the skull and long bones, and the clinical findings and normal blood counts did not substantiate this diagnosis. Serologic studies and a Mantoux test gave negative results. The roentgenogram of the chest showed that it was normal. No diagnosis was established. The patient was clinically well and is being observed on an outpatient status.

Roentgenograms of the wrists were taken of 351 patients observed in the private practice of one of us (M. G. P.). The age range was 6 months to 16 years. In general the same criteria for diagnosis were required whenever practicable. Of the total number of patients studied, 35 presented pathologic findings on visualization of the wrists by roentgen ray. This constituted 9.97 per cent of the total number of observations made. Evidence of rickets was noted in 6. There were 24 patients who had evidence of delayed ossification according to the Leonard "ossification index." This group constituted 6.84 per cent of the total number of cases. Fourteen of the patients had hypothyroidism, and of these 2 had an accompanying allergy. Three had cerebral birth injury with convulsions, 3 had retardation of undetermined cause (1 of whom had an accompanying allergy), 1 was mentally retarded, 1 had fibrocystic disease of the pancreas, 1 was a

pituitary dwarf, and 1 had evidence of cerebral dysgenesis with hypothyroidism. There were 2 patients with mongoloidism who showed a cuboidal formation of the middle phalanx of the little finger on the roentgenograms. The next case in this series was one of lead intoxication. Definite heavy metal (lead?) lines were seen in the distal metaphyses of the ulnas and radiuses.

Also in this group there was 1 patient with chondrodystrophy in whom the roentgenograms revealed typical skeletal changes in the hand. The last case in this series was one of pubertas precox in a boy aged 4 years. The patient exhibited precocious secondary sexual development of enlarged penis and scrotum with pubic hair. The "ossification index" in this case was advanced to that of an 8 year old child.

It may be noted that a total of 3 patients in this group had an accompanying allergy along with a delay in the ossification index. It is not feasible to discuss the individual cases in this series.

COMMENT

Six hundred and eighty-four infants and children were investigated for evidence of a pathologic process by means of routine roentgenograms of the wrists. Three hundred and thirty-three patients were studied in the Milwaukee County Pediatric Service. Three hundred and fifty-one were observed in private practice. Thirty-four or 10.21 per cent of the patients studied in the Milwaukee County Pediatric Service and 35 or 9.97 per cent of the patients studied in private practice had evidence of abnormalities in the roentgenograms of the wrists. For means of determining a delay in the centers of ossification the revised Leonard "ossification index"[19] was used exclusively. According to this index, which deals with the latest possible time of appearance of these bones, the capitate bone appears at 6 months, hamate bone at 7 months, distal radial epiphysis at 2 years, triquetrium bone at 4 years, lunate bone at 5 years, navicular bone at 6 years, the greater and lesser multangular bones at 7 years and the distal epiphysis of the ulnar bone at 8 years. A full complement of the bones for a normal eight year old child would be as follows: 8-67-2456778. As has been stated previously in this paper by Leonard,[19] a delay according to the "ossification index" would reveal definite abnormality in skeletal maturation.

A number of pathologic findings were visualized which were consistent with the following conditions: rickets, hypothyroidism (delayed ossification), cerebral birth injury (delayed ossification), mental retardation (delayed ossification), fibrocystic disease of the pancreas (delayed ossification), pituitary dwarfism (delayed ossification), cere-

bral dysgenesis with hypothyroidism (delayed ossification), delayed ossification (cause undetermined), scurvy, syphilis, lead intoxication, mongoloidism, osteochondromatosis, chondrodystrophy, pubertas precox, and osseous changes not attributable to any definite clinical entity.

Our investigation indicates that the routine roentgenogram of the wrist is warranted for all children seeking medical attention. This is not only a valuable procedure as a diagnostic aid but frequently an informant of occult pathologic processes. Roentgenologic interpretation of this small, revealing anatomic area can be made with a considerable degree of accuracy. This procedure is simple and harmless and consumes little technical time.

SUMMARY

1. A study in the routine use of roentgenograms of the wrist for 684 infants and children has been presented.

2. Two series were done independently, one in a private pediatric practice, and the other in a charity hospital pediatric service.

3. Of 333 hospital cases 34 or 10.21 per cent and of 351 private patients studied 35 or 9.97 per cent of the roentgenograms of the wrists revealed evidence of a pathologic process.

4. At least 14 entities were discussed in which there was evidence of abnormality in the roentgenograms of the wrists.

Drs. J. L. Marks and A. Nathan gave us their cooperation in this investigation.

DYSOSTOSIS OF SKULL, FACE AND EXTREMITIES (ACROCEPHALOSYNDACTYLY)

ROBERT W. BUCKLEY, M.D.
CINCINNATI
AND
PAUL I. YAKOVLEV, M.D.
MIDDLETOWN, CONN.

IN CONNECTION with the study of a recently observed case of acrocephaly, facial deformities and syndactylism, with mental deficiency, the literature pertaining to clinical descriptions of similar cases was reviewed.

REPORT OF A CASE

History.—J. C., a white boy of Italian parentage, was admitted to the Walter E. Fernald State School on July 5, 1943, at the age of 12 years, because of asocial behavior and gross physical deformity. He was born June 20, 1931, the youngest of seven children. The birth was one month premature but otherwise normal; multiple physical defects were obvious at birth. Nursing was difficult because of cleft palate; he had daily convulsions from the age of 2 days to 4 years. Development was retarded, with teething at 1 year, walking at 2½ years, and poorly articulate speech at 4 years. He had uncomplicated measles, mumps, chickenpox and pneumonia before the age of 5 years. He never attended public school and presented a behavior problem by attacking smaller children, voiding in public, stealing, running away and incurring persecution by other children because of his bizarre appearance and conduct.

The child's mother (aged 52 at time of interview) was an obese white woman who showed an asymptomatic swelling of the thyroid without exophthalmos; she was of normal mental development and had no other physical stigmas. The family history, including the child's father (deceased at 61), six older siblings, and maternal and paternal grandparents, when reviewed in detail gave no indication of characteristic physical deformities or mental deficiency.

Physical Examination.—Examination of the child (January 1947) showed a strikingly ugly boy who was small for his age (height 60¼ inches [153 cm.]; weight 87 pounds [39.5 kg.]) and who walked with a peculiar waddling and hopping gait. The skull was high and broad, with a transverse bony ridge at the uppermost point, which was found anterior to the frontoparietal junction (figs. 1*A* and 2). The fontanels were closed. The transverse (biparietal) diameter was 15.4 cm.; the anteroposterior (occipitobregmatic) diameter was 16.5 cm.; the circumference was 53.7 cm. and the cephalic index was 0.93. There was severe proptosis of both eyeballs with limitation of extraocular movements and divergent squint. The orbits

From the Research Unit and Hospital-Infirmary Division, Walter E. Fernald State School, Waverley, Mass.

were shallow; the zygomata were rudimentary in size and shape. The nose was short and saddle-shaped; the upper lip was short. The teeth were bizarre in shape and distribution, with multiple duplications, and set in markedly wide alveolar surfaces of both jaws (fig. 3*B*). The anterior portion of the hard palate was narrow and acutely arched; the posterior half was cleft, with a distinct uvula on each half. The lower jaw was moderately prognathous.

Both humeri were short, with a good range of motion associated with winging of the scapulas. There was slight bowing of the femurs, with bilaterial genu valgum. The hands and feet showed complete fusion (syndactyly) of all digits except the

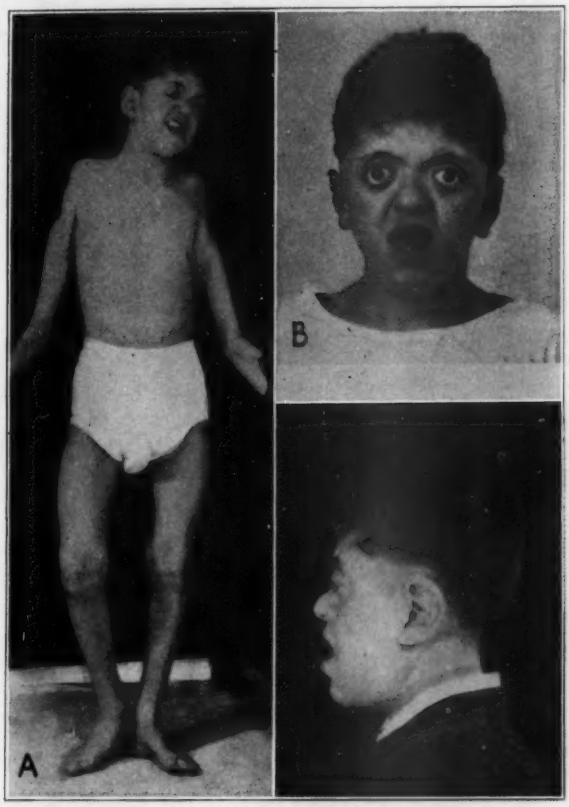

Fig. 1.—Multiple views of patient showing stigmas.

thumbs and great toes; the nails were flat, misshapen and partially fused. All digits were almost completely extended and could not be flexed actively or passively (fig. 3*A*).

The musculature was poorly developed; neurologic examination showed no paralysis or contractures; examination of the internal organs and routine laboratory procedures gave no abnormal results. On mental examination, the boy was found to be a cooperative and fairly social imbecile. His speech was nasal and poorly articulate. He required assistance in feeding and dressing himself, as his syndactylism made impossible digital manipulations. Intelligence quotients over a period of three and one-half years have remained about 30 on the Stanford-Binet scale.

Roentgen Examination.—Roentgenograms of the skull, right humerus and feet (figs. 2 and 4) are presented as typical of the deformities found throughout the skeleton. The left lateral view of the skull shows the high crested appearance of the calvarium, the characteristic "lacunar" defects of the frontal region, the shallow orbits, dental anomalies and prognathism. There is an apparent fusion of the spinous processes of the fifth and sixth cervical vertebrae. The head of the right humerus is translucent, with a thin cortex and expanded and deformed outline; it appears fused to the glenoid portion of the scapula, with radiating dense bony spicules continuous with similar structures on the blade of the scapula. The distal extremity of the humerus shows normal density and persistent epiphysial separation. The shaft is short and bowed. Posteroanterior views of both feet show "condensation" of the phalanges of each digit, with preservation of the proximal

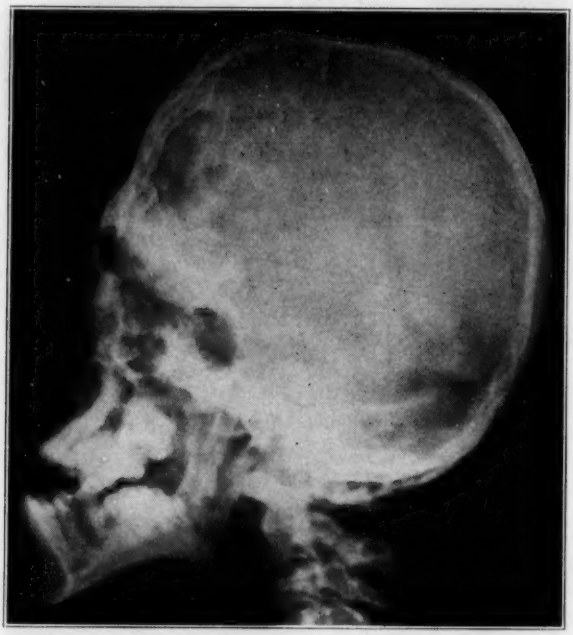

Fig. 2.—Roentgenogram of right side of skull.

epiphyses, but only indistinct separation distally. The first and second metatarsals are grossly deformed bilaterally; the left second metatarsal is angulated laterally with local density suggesting an old fracture, and the right first and second metatarsals are united by a broad, bony band with anomalous articulation of the first on the ankle. Roentgenograms of the left shoulder and hands showed analogous deformities.

HISTORICAL REVIEW

Survey of the literature reveals numerous cases in which different features of the case described were present in several combinations. This boy's set of physical and mental anomalies would appear to represent a complete picture, parts of which have been reported under

various clinical names and personal eponyms. Complete citation of all cases reported is not attempted here, since much of the original material has appeared in older foreign literature which is relatively unavailable. The key publications referred to, however, are selected from reports totaling approximately 139 cases of acrobrachycephaly with and without syndactylism. The entity—for it has been repeatedly

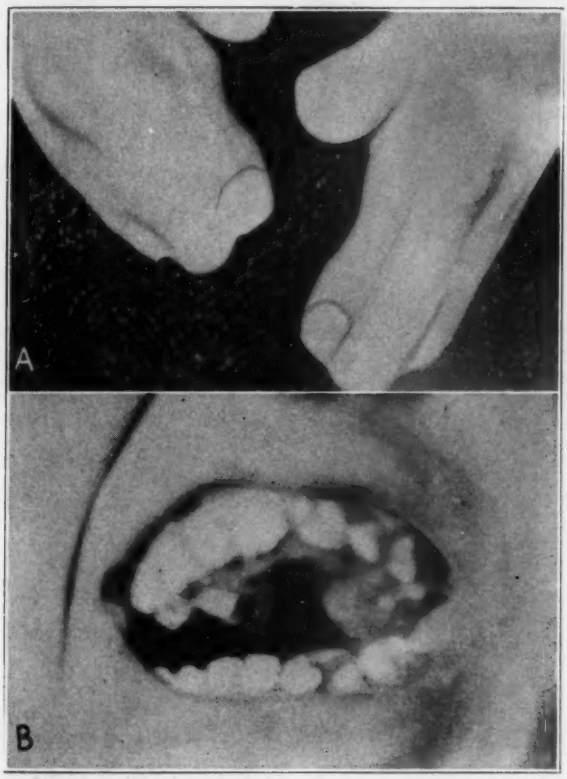

Fig. 3.—*A*, dorsal view of hands showing fusion of digits and finger nails; *B*, mouth, demonstrating dental irregularities and cleft palate.

demonstrated to be more than a chance combination of physical deformities — has been variously called "acrocephalosyndactylia" (Apert[1]) and "acrosphenodactylia" (Maygrier[2]); in cases not showing syndactylism it has been called "craniofacial dysostosis" (Crou-

1. Apert, E.: De l'acrocephalosyndactylie, Bull. et mém. Soc. méd. d. hôp. de Paris **23**:1310, 1906.

2. Maygrier: Presentation d'un enfant atteint de malformations du crane (porencephalie) et des extremities (syndactylie) par heredo-syphilis, Bull. et mém. Soc. méd. d. hôp. de Paris **33**:545, 1912; cited by Crouzon.[3]

zon[3]), and eponyms of "Crouzon's disease" and "Apert's disease" have been repeatedly applied, especially in the French and Latin-American literature.

The original description of acrocephalosyndactyly appears to have been made by Troquart[4] in 1886; this and 8 other cases were gathered

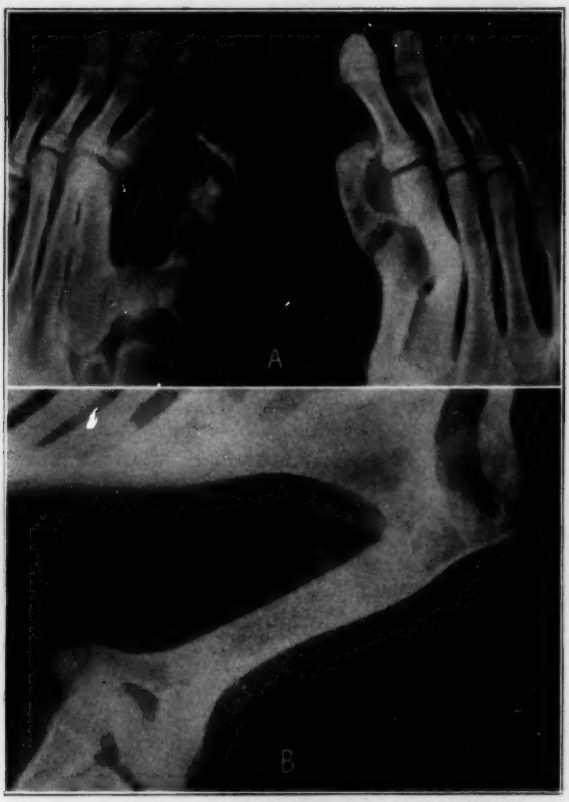

Fig. 4.—*A*, roentgenogram of feet in anteroposterior direction, showing multiple bony anomalies; *B*, left humerus in anteroposterior position, showing bowed shaft and synostoses.

from the literature and personal experience by Apert[1] in 1906. Rather curiously, the group of cases first described by Crouzon[5] in 1912, and summarized in 1929[3] under the name craniofacial dysostosis, was not particularly mentioned as being related to the earlier cases which

3. Crouzon, O.: Dysostose cranio-faciale, in études sur les maladies familiales nerveuses et dystrophiques, Paris, Masson & Cie, 1929, pp. 278-344.

4. Troquart, R.: Syndactylie et malformations diverses, Mém. et bull. Soc. de med. et chir. de Bourdeaux, 1886, p. 69; cited by Apert.[1]

5. Crouzon, O.: Dysostose cranio-faciale héréditaire, Bull. et mém. Soc. méd. d. hôp. de Paris **33**:545, 1912; cited by Crouzon.[3]

showed the same stigmas as those of Crouzon, with the addition of syndactylism; since no more recent literature has been found which describes the conditions as identical, it is believed that the present report is the first complete grouping of these cases under one heading. (Park and Powers[6] and Valentin[7] gave extensive reviews of the cases of acrocephaly and syndactylism of Apert's type, but did not identify them with "Crouzon's disease.")

The physical and roentgen findings of acrocephalosyndactyly have been thoroughly described by Park and Powers[6]. They emphasize that

> The head is abnormally high, short and broad. The occiput is almost flat. The eyeballs protrude and have the appearance of being obliquely set in such a manner than their transverse axes are inclined outward and slightly downward . . . The vertical diameter of the head is greatly increased and . . . The increased height is due to an abnormal extension upwards of the cranial vault . . . The head relatively and actually is broad . . . The nose has been variously described as "large and thick," "flat and depressed," "the root depressed or flattened," "short and broad," "small and thin," . . . The mouth is open; the middle portion of the upper lip is elevated, and occupies a more forward position than normal . . . The hard palate was extremely narrow and high . . . in at least five of the cases the hard palate was cleft . . . in the majority of subjects beyond the age of infancy dentition was abnormal . . .

Their additional description of the types of syndactyly varied from complete fusion of all fingers and toes to various combinations of partial fusion. The photograph of the patient in a case reported by Gadelius[8] showed finger nails more completely fused than those of our patient. Synostoses and synarthroses of the shoulders and elbows were described as frequent findings by Park and Powers. Intelligence was believed to be normal in the majority of reported cases.

Crouzon's[3] descriptions of the cranial and facial anomalies tally closely with the summarized findings of Park and Powers. It is interesting to note in this connection that Crouzon reviewed 4 hereditary and familial instances of craniofacial dysostosis. This would seem to differentiate the syndrome from acrocephalosyndactylism, since Valentin[7] stated in 1938 that "so far the world literature has not presented a single case of pure acrocephalosyndactylism in which heredity or familial occurrence of exactly the same malformation has been

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6. Park, E. A., and Powers, G. F.: Acrocephaly and Scaphocephaly with Symmetrical Malformations of the Extremities, Am. J. Dis. Child. **20**:255 (Oct.) 1920.

7. Valentin, B.: Die Korrelation (Koppelung) von Missbildungen, erläutert am Beispiel der Akrocephalosyndaktylie, Acta orthop. Scandinav. **9**:235, 1938; cited by Cohn, B. N. E.: True Oxycephaly with Syndactylism, Am. J. Surg. **68**:93, 1945.

8. Gadelius, B.: En sällsynt form af idioti med karakteristiska utvecklingsanomalien: Akrocephalosyndaktyli (Apert), Nord. med. ark. **15**:1, 1915; cited by Park and Powers.[6]

described." In a publication by Weech[9], however, the occurrence of identical deformities in mother and daughter is described, with the suggestion that "the combined malformations are evidences of germ plasm defects rather than the result of externally operating causes".

Etiology and pathogenesis of these conditions are discussed at varying lengths in the foregoing and other publications[10]; the theories are voluminous, complex and inconclusive.

The roentgen findings do suggest some diffuse abnormality of bony growth and union, not restricted either to "membranous" or to "cartilaginous" bony anlage. The abnormalities are always present in some degree of development at birth, and have definitely been found in hereditary and familial incidence. The cranial deformities have been attributed to premature obliteration of sutures by some and to inflammatory disease of the embryonic osteogenic membranes by others, notably by Crouzon[3]. The frequently but not invariably associated mental deficiency seems most reasonably ascribed to compressions of the growing brain, particularly in the anteroposterior direction.

There would seem, on the basis of reports to date, to be no definite racial incidence of this syndrome; cases have been reported in Latin, Nordic and Negro subjects. Maternal syphilis and alcoholism are not significant factors.

SUMMARY AND CONCLUSIONS

One case is presented of congenital acrocephalosyndactylism associated with mental deficiency in a 12 year old white boy without any obtainable family history of similar developmental anomalies.

The literature pertaining to acrocephaly, proptosis of the eyeballs and facial anomalies, with and without deformities of the extremities, is briefly reviewed; the opinion is expressed that "Apert's disease", or acrocephalosyndactylism, and "Crouzon's disease", or craniofacial dysostosis, are both manifestations of the same pathologic situation.

The condition of faulty bone development and articulation is believed to be due to a germ-plasm defect influencing the growth of both "membranous" and "cartilaginous" bone.

9. Weech, A. A.: Combined Acrocephaly and Syndactylism Occurring in Mother and Daughter, Bull. Johns Hopkins Hosp. **40**:73, 1927.

10. Sirkin, J.: Acrocephalosyndactylia, Am. J. Ment. Deficiency **48**:335, 1944. Ruh, H. O.: Acrocephalosyndactylism: A Teratological Type, Am. J. Dis. Child. **11**:281 (April) 1916. Davis, B. F.: Acrocephalosyndactylism, ibid. **9**:446 (May) 1915.

Case Reports

SEVERE ERYTHEMA MULTIFORME (STEVENS-JOHNSON SYNDROME) IN CHILDHOOD

JORGE E. HOWARD, M.D.
Resident in Medicine at the Children's Memorial Hospital
SANTIAGO, CHILE
AND
SYDNEY PEDVIS, M.D.
MONTREAL, CANADA

IN 1922 Stevens and Johnson reported 2 cases under the title "an eruptive fever with stomatitis and ophthalmia."[1] These patients were boys 7 and 8 years of age, and in both children after a period of three to four weeks the temperature fell to normal, the cutaneous lesions disappeared and the general condition improved. The sequelae were in 1 instance a severe corneal ulcer and in the other bilateral panophthalmitis with destruction of the cornea and lens.

The combination of cutaneous lesions, involvement of the mucous membranes and severe constitutional symptoms was first reported in medical literature in 1822 by Alibert and Bazin.[2] Von Hebra in 1866, in his original description of erythema multiforme bullosa, also mentioned cases with conjunctival and oral changes.[3] In the subsequent years many authors, unfortunately, reported cases with similar symptoms under various names. Hence, "ectodermose erosive pluriorificielle,"[4] "dermatostomatitis,"[5] "Stevens-Johnson disease,"[6] "Behcet's syndrome"[7] and "mucosal respiratory syndrome"[8] are all conditions

From the Children's Memorial Hospital, Montreal, Canada; Physician in Chief, Dr. Alton Goldbloom.

1. Stevens, A. M., and Johnson, F. C.: A New Eruptive Fever Associated with Stomatitis and Ophthalmia, Am. J. Dis. Child. **24**:526 (Dec.) 1932.

2. Alibert and Bazin, cited by Rosenberg, I., and Rosenberg, J.: Erythema Exudativum Multiforme (Hebra) with Conjunctivitis and Stomatitis, Arch. Dermat. & Syph. **41**:1066 (June) 1940.

3. von Hebra: Diseases of the Skin, translated and edited by C. H. Fagge, London, New Sydenham Society, 1866, vol. 1.

4. Rendu, R.: Sur un syndrome caracterisé par l'inflammation simultanée de toutes les muqueuses externes (conjonctivale, nasale, linguale, bucco-pharyngée, anale et balano-préputiale) coexistant avec une éruption varicelliforme puis purpuri que des quatre membres, Rev. gén. de clin. et de thérap. **30**:351, 1916.

5. Baader, E.: Dermatostomatitis, Arch. f. Dermat. u. Syph. **149**:261, 1925. Low, E. B., and Davies, J. H. T.: Dermatostomatitis (Baader) Complicating a Case of Manic Depressive Insanity, Brit. J. Dermat. **50**:141, 1938.

6. Murphy, R. C.: An Eruptive Fever Involving the Mouth and Eyes (Stevens-Johnson's Disease), New England J. Med. **230**:69, 1944.

7. Prosser Thomas, E. W.: Behcet's Syndrome, Brit. M. J. **1**:14, 1947.

8. Stanyon, J. H., and Warner, W. P.: Mucosal Respiratory Syndrome, Canad. M.A.J. **53**:427, 1945

that have in common the triad of cutaneous, ocular and mucous membrane lesions. These lesions are associated with general toxicity and differ only in the predominance of one or other of the principal symptoms. The modern concept is that all these cases, except possibly those reported as Behcet's syndrome, were instances of severe erythema multiforme with predominant involvement of the mucous membranes.

Severe erythema multiforme (Stevens-Johnson syndrome) is a clinical entity of unknown origin. Some authors expressed the belief that it is a virus disease, while others classified it as an allergic, or even a toxic, condition. Virus studies have not proved conclusive. In the cases reported by Stanyon and Warner[8] and by the Commission on Acute Respiratory Diseases[9] extensive virus antibody studies were undertaken but showed no evidence of virus infection. Because of the peculiar distribution of the lesions, the herpes virus was suggested as a possible etiologic agent,[10] but never have herpetic virus antibodies been demonstrated.[11] The experimental studies of Edgar and Syverton[12] seem to favor an anaphylactic mechanism as the basis for the syndrome; however, their work was done with vesicular fluid drawn from only 1 patient; hence its significance is limited. Recently, Schoemperlen[13] reported a case of "mucosal respiratory syndrome" in which treatment with diphenhydramine ("benadryl") hydrochloride was successful. This successful therapy and the fact that several patients were known to have repeated attacks of the syndrome could be offered in support of the aforementioned theory. Goldfarb, in reviewing the Stevens-Johnson syndrome,[14] observed eosinophilia in only 2 cases. This fact is not in keeping with an allergic type of mechanism.

The histologic studies made on biopsy specimens of the cutaneous lesions showed nonspecific inflammatory changes and therefore did not further knowledge of the origin of erythema multiforme. No inclusion bodies, suggesting a virus origin, have ever seen seen.

The symptoms of severe erythema multiforme develop abruptly, the first signs to appear being hyperthermia, headache and general toxicity, followed by cutaneous lesions. The lesions are at first macular and papular and vary from 0.5 to 6 cm. in their longest diameter. These macules and papules tend to become vesicular and rupture easily, leaving a firm, adherent hemorrhagic crust. The evolution

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9. Association of Pneumonia with Erythema Exudativum Multiforme, Commission on Acute Respiratory Diseases, Fort Bragg, N. C., Arch. Int. Med. **78**:687 (Dec.) 1946.

10. Forman, L., and Whitwell, G. P. B.: Erythema Exudativum Multiforme, Brit. J. Dermat. **46**:309, 1934.

11. Rook, A.: Association of Erythema Multiforme with Herpes Simplex, Brit. M.J. **1**:138, 1947.

12. Edgar, K. J., and Syverton, J. T.: Erythema Exudativum Multiforme with Ophthalmia and Stomatitis: Report of Two Cases in Children with Certain Observations on Histopathology and Animal Innoculation, J. Pediat. **12**:151, 1938.

13. Schoemperlen, C. B.: Mucosal Respiratory Syndrome Treated with Benadryl, Canad. M. A. J. **56**:73, 1947.

14. Goldfarb, A. A.: A Case of Stevens-Johnson Disease (Erythema Multiforme Bullosa) Treated with Penicillin, J. Pediat. **28**:579, 1946.

from macular to hemorrhagic lesions in severe cases may take only a few days, while in others it occurs over two or three weeks. The lesions predominate on the extremities, are less abundant on the thorax and abdomen and are never present on the scalp. After this first manifestation, no new lesions develop, and those present slowly disappear without scarification. Several authors reported cases of "erythema multiforme" with mucous symptoms but without cutaneous lesions.[15]

The mucous membrances may be involved from the onset, but generally the lesions do not appear before the third day. The conjunctival and oral mucosas are usually the most severely involved, but in many cases the mucosa lining the respiratory tract, the anus or the glans penis is also affected.[16] In the mouth the lesions appear as vesicles which are implanted on an erythematous base. Later, these vesicles rupture and cause erosions, which are soon covered with a grayish white pseudomembrane. In most cases the lesions do not progress further, and healing takes place. In other instances the bullae are numerous, and when they break down erosions are formed on the tongue, lips and pharynx. Occasionally, these erosions are present on the trechea and bronchi and produce a sticky sanguinopurulent discharge, which may cause obstruction and which also may result in pneumonia.[8]

The conjunctival lesions of erythema multiforme were extensively studied by Duke-Elder,[17] who distinguished three major forms. The first and commonest form is the catarrhal, which generally heals within two weeks without sequelae. The second and rarest type is a purulent conjunctivitis, which is the severest form since it may result in grave complications—corneal perforation and secondary panophthalmitis. To this group belong the original 2 cases described by Stevens and Johnson,[1] and, therefore, in its strictest sense, the eponym "Stevens-Johnson syndrome" should be applied only to cases with purulent conjunctivitis.[18] At present, with the antibiotic substances the suppuration can be checked in its early stages, thus preventing perforation. The third form is a pseudomembranous conjunctivitis, in which membranes form on the tarsal conjunctiva. These membranes may heal rapidly[19] or may progress to lesions which persist for many years.[20]

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15. Butler, J.: Erythema Multiforme Confined to the Mucous Membranes, Arch. Dermat. & Syph. **6**:1 (July) 1922. Mach, R. S.; Babel, J., and Naville, M.: Syndromes muco-cutanés avec complications oculaires (érythème polymorphe, iritis récidivante aphtheuse), Helvet, med. acta **7**:552, 1941.

16. Klauder, J. V.: Ectodermosis Erosive Pluriorificialis: Its Resemblance to the Human Form of Foot and Mouth Disease and Its Relation to Erythema Exudativum Multiforme, Arch. Dermat. & Syph. **36**:1067 (Nov.) 1937.

17. Duke-Elder, W. S.: Erythema Exudativum Muliforme (Hebra), in Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1733.

18. Ginandes, G. J.: Eruptive Fever with Stomatitis and Ophthalmia, Am. J. Dis. Child. **49**:1148 (May) 1935.

19. Koke, M. P.: Conjunctivitis in Erythema Exudativum Multiforme, Arch. Ophth. **25**:78 (Jan.) 1941.

20. Rutherford, C. W.: Membranous Conjunctivitis with Loss of the Eyeballs, J.A.M.A. **93**:1779 (Dec. 7) 1929.

Lesions in other organs were described as "erythema multiforme,"[21] but apparently these cases were not true instances of the condition.

The symptoms reach a peak at about the fourth or fifth day and remain at this stage for a few days. Recovery begins with the disappearance of the lesions in the mouth, followed in some cases by improvement in the active phase of the conjunctivitis. The temperature returns to normal at about the fifteenth day, and shortly afterward the cutaneous manifestations begin to recede.

The reported results of laboratory studies were not conclusive. The white blood count showed no consistent change, and differential counts were noncontributory. Cultures taken from the lesions of the skin, mouth and conjunctiva grew many nonspecific organisms.

In the differential diagnosis, according to Lever[22] the following conditions are important: 1. Pemphigus vulgaris, the onset of which is not so abrupt; it occurs in an older age group and has a different course. 2. The human form of foot and mouth disease, a condition characterized by swelling, redness and desquamation about the nails of hands and feet. In doubtful cases the inoculation of laboratory animals will prove the diagnosis. 3. Toxic eruptions due to drugs (especially the sulfonamide compounds)[23] and foods to which the history and course will give a clue.

The treatment of this syndrome is still under discussion. The cutaneous lesions are of little importance, since they are self limited. However, attention should be focused on the prevention of the purulent conjunctivitis and its severe sequelae. Several authors reported favorable results in this respect following the use of sulfadiazine.[24] Penicillin administered systemically and instilled locally into the conjunctival sac also was used with good results.[14] Schoemperlen reported the successful use of diphenhydramine hydrochloride in 1 case. This observation needs further study for proper evaluation.

REPORT OF A CASE

S. L., a 1 year old girl, was admitted to the Children's Memorial Hospital for the first time on Dec. 19, 1946 with the following history: The child was apparently well until December 14, five days before admission, when she became acutely ill; her temperature rose to 41 C. (105.8 F.), and she had several generalized convulsions. A few hours later the mother noted many indurated, macular, hemorrhagic cutaneous lesions of irregular shape. These lesions were more prominent

21. Osler, W.: On the Visceral Complications of Erythema Exudativum Multiforme, Am. J. M. Sc. **110**:629, 1895; On the Visceral Manifestations of the Erythema Group of Skin Diseases, ibid. **127**:1, 1904.

22. Lever, W. F.: Severe Erythema Multiforme: Report of Two Cases of the Type Ectodermosis Erosiva Pluriorificialis, with Development of Cicatricial Conjunctivitis and Keratitis in One Case, Arch. Dermat. & Syph. **49**:47 (Jan.) 1944.

23. Raffelo, J. F., and Nichols, J.: A Nearly Fatal Reaction to Sulfadiazine in a Ten Year Old Girl Involving Skin, Eyes and Oropharynx, J. Pediat. **20**:753, 1942. Greenberg, S. I., and Messer, A. L.: Fatal Bullous Dermatitis, Following Administration of Sulfadiazine, J.A.M.A. **122**:944 (July 31) 1943.

24. Ageloff, H.: Erythema Multiforme Bullosum with Involvement of the Mucous Membranes of the Eyes and Mouth (Stevens-Johnson Disease), New England J. Med. **223**:217, 1940.

on the extremities and face, less noticeable on the abdomen and trunk and absent from the scalp. At this time she was vomiting all her feedings and looked severely ill. On the following day her temperature remained at about 40 C. (104 F.); she was more toxic, and fresh cutaneous lesions were noted. In addition, the left eye was swollen; the cornea appeared dull, and a purulent discharge drained from the inner canthus. Pronounced edema of the hands and feet appeared for the first time on the third day of illness. The skin over these areas was cold and glistening. As these symptoms persisted and as the child's general condition was poor, she was brought to the outpatient department, whence she was referred for immediate admission.

The only treatment that this child received prior to admission was 0.30 Gm. of acetylsalicylic acid U. S. P. on the third day of illness. The family history was irrevelant, and no history of allergy could be obtained.

Physical examination on admission to the hospital showed a well developed and well nourished child who appeared to be acutely and severely ill. She was irritable and resisted examination. The rectal temperature was 39.4C. (102.9F.), the pulse rate was 115 and the respiratory rate 30 per minute. There were numerous red, indurated macular and papular lesions on the face, arms, buttocks and legs. Many of these lesions were covered with hemorrhagic crusts, and interspersed among them were firm subcutaneous nodules and a few small, fading ecchymotic areas. The lesions were of varied shapes and ranged from 0.5 to 2.5 cm. in diameter. The only other significant findings on physical examination were the following changes: The posterior part of the right ear drum membrane bulged and showed slight reddening. The conjunctiva of the left eye was extremely injected, and the left fundus could not be visualized, owing to an opacity. There were small bullae on the tongue and palate and the mucosa of the cheeks and a soft, pitting edema limited to the hands and feet.

Laboratory Studies.—The results of the laboratory tests are given in the table.

Results of Laboratory Tests

Blood:	Hemoglobin, Gm./100 Cc.	White Blood Cells	Polymorphonuclear Leukocytes	Lymphocytes	Monocytes	Eosinophils	Stab Forms
Dec. 19	6.9	22,350	9,387	11,622	894	0	447
Dec. 23	8.3	23,300	16,310	6,058	932	0	0
Jan. 4	10.5	12,500	7,000	5,000	250	0	0

Cholesterol	139 mg./100 cc.
Wassermann reaction of blood	negative
Nonprotein nitrogen	14 mg./100 cc.
Total proteins	5.37 Gm./100 cc.
Albumin	3.20 Gm./100 cc.
Globulin	2.17 Gm./100 cc.
Albumin-globulin ratio	1.5

These values for the blood chemistry are normal.

Cultures: Cultures of material from the eye, nose and throat and of the urine blood and cerebrospinal fluid revealed no pathogenic organisms present. The bullae yielded a light growth of Staphylococcus pyogenes organisms and a heavy growth of micrococci.

Urine: Urinalyses showed nothing abnormal.

Tuberculin Tests: Reactions to the Mantoux test (0.1 mg.) and to the test with old tuberculin were negative.

Spinal Fluid: On December 21, crystal-clear spinal fluid was taken under normal pressure. It contained 20 cells per cubic millimeter, all lymphocytes. Proteins measured 44.3 mg. and sugar 70.7 mg., per hundred cubic centimeters.

Roentgenographic Findings: Studies made on December 26 showed "no evidence of active intrathoracic disease." Additional roentgenographic studies of the long bones revealed "no evidence of rickets, scurvy or syphilis" (Dr. D. L. McRae).

Biopsy.—A biopsy specimen of a healing cutaneous lesion from the posterior aspect of the left calf was removed on Jan. 4, 1947 (three weeks after onset of cutaneous lesions). Microscopic examination showed slight acanthosis and fairly definite hyperkeratosis in the epidermis and corium, while the corium also showed focal dilatation of the capillaries and venules. These vessels were surrounded with a narrow zone of mononuclear cells and active fibroblasts. Slight scarring on the corium probably occurred, although this was difficult to assess, as it was minimal. The subcutaneous tissues showed the most definite and most interesting changes, although one cannot be dogmatic as to their interpretation or specificity. The fibrous trabeculae were widened from scarring, with irregular, fine collateral scars running between the fat cells. An occasional trabecula contained thin, irregular foci of histiocytes (macrophages?), associated with a few lymphocytes, neutrophils and eosinophils. There was an irregular, focal proliferation of connective tissue between the fat cells. In these areas were small numbers of large, granular "foam cells" (presumably lipid-laden macrophages). These cells often lined an empty space, which may have contained neutral fat. In one area small, irregular acidophilic masses of degenerated tissue were seen, associatd with a few small macrophages. This area was possibly a small focus of degeneration of ordinary fat cells. Nowhere was there evidence of fat necrosis, and yet the histologic appearance of the lesion suggested that the subcutaneous fat cells had previously been somewhat damaged. No hemosiderin pigment was indentified.

The lesion in this case was characterized by minimal cutaneous changes and pronounced subcutaneous scarring. The scarring was associated with focal collections of lipid-containing macrophages, apparently secondary to damage to the neutral fat cells. The lesions of the subcutaneous tissue are unusual but certainly, at present, cannot be interpreted as specific for this disease.

Course in the Hospital.—On her admission therapy with penicillin (25,000 units every three hours) and sulfadiazine (1.40 Gm. daily) was instituted.

Because of the anemia, a transfusion of 100 cc. of whole blood was given immediately. This procedure was repeated the following day. On the third day the conjunctivitis seemed worse, and penicillin eye drops (1,000 units per cubic centimeter) were prescribed.

For the first five days the child was severely ill, looked toxic and accepted only fluids. Despite the chemotherapy, the temperature ranged from 39 to 40 C. (102.2 to 104 F.) for the first week and reached normal only on the tenth day in the hospital. On the second and third day fresh cutaneous lesions were noted. These new lesions were vesicular and hemorrhagic and ruptured within a few hours, leaving crusted areas.

On the fifth day in the hospital the consulting ophthalmologist, Dr. A. B. Alexander, examined the patient. He reported: "The right disk is somewhat pale, most probably because of the anemia present. The retina is thin. The left lens is clear, but the many gross and small opacities present in the vitreous suggest a posterior uveitis. Fundal details are not clear. The diagnosis is posterior uveitis of the left eye."

After six days, in view of her general improvement, the sulfadiazine was discontinued and the dose of penicillin reduced to 10,000 units every three hours. The lesions in the mouth began to recede shortly after her admission and had completely disappeared by the fifth day in the hospital. About this time the cutaneous lesions were losing their crusts, leaving a pale discolored area. The edema of the hands and feet that was noticed on her admission persisted to a varying degree for seven days.

On the nineteenth day in the hospital she was again examined by Dr. Alexander: "The vitreous of the left eye is now much cleared, and fewer opacities and floaters are present in the vitreous. The optic disk is normal. The retina is still seen through a haze, but no gross pathologic changes are noted. In view of the rapid clearing of the vitreous, in my opinion a hemorrhage into the vitreous was the most probable cause of the ocular lesion."

By the third week the cutaneous lesions had completely disappeared, and the child's general condition was good. She was seen for the third time by Dr. Alexander two weeks later. He stated: "The right fundus is normal. In the left eye, the lens is clear. The opacities in the vitreous are much less evident. The disk and fundus are apparently normal, though the disk still looks hazy (but clearer than before), most probably because of opacities. Rapid recovery of the eye would tend to confirm the last impression of a hemorrhage into the vitreous as the most probable diagnosis."

The child progressed satisfactorily. On February 2 she contracted chickenpox and was treated for four days at a hospital for infectious diseases.

COMMENT

This case of severe erythema multiforme presents the three principal groups of symptoms, involving the skin, eyes and mouth, which are characteristic of the condition. Several features are interesting. The case occurred in one of the youngest patients so far reported on.[25] The usual course of the disease was not significantly altered by treatment, even though large doses of sulfadiazine and penicillin were used. The edema of the hands and feet in the presence of normal plasma protein levels, and without evidence of disease in the cardiovascular and renal systems, is a point in favor of the theory of an allergic mechanism. Hemorrhages in the vitreous have not been noted in cases of severe erythema multiforme; however, Katzenellenbogen[26] reported a case of the so-called Behcet's syndrome, to which we refered in the introduction, as an allied condition.

In the literature reviewed, only one author, Fanconi,[27] reported the results of an examination of the spinal fluid. He mentioned an elevated protein level (43 mg. per hundred cubic centimeters) with an accompanying pleocytosis of 14 lymphocytes. These results are similar to ours (protein, 43.4 mg. per hundred cubic centimeters and lymphocytes, 20 per cubic millimeter).

SUMMARY

A case of severe erythema multiforme (Stevens-Johnson syndrome) in a 1 year old child is reported. The important features of this syndrome are reviewed. Intensive treatment with penicillin and sulfadiazine resulted in the healing of the ocular lesions without sequelae.

Hospital "Luis Calvo Mackenna."

Dr. F. W. Wiglesworth interpreted the biopsy of the skin.

25. Landott, R. F.: Ectodermosis Erosiva Pluriorificialis in Infant Four Weeks Old, Helvet. pediat. acta **1**:263, 1946.

26. Katzenellenbogen, I.: Recurrent Aphthous Ulceration of Oral Mucous Membrane and Genitals Associated with Recurrent Hypopyon Iritis (Behcet's Syndrome), Brit. J. Dermat. **58**:161, 1946.

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CUTIS ELASTICA

(Dermatorrhexis, Ehlers-Danlos Syndrome)

L. G. PRAY, M.D.
FARGO, N. D.

EHLERS[1] and Danlos[2] are responsible for recognizing and describing this syndrome in its entirety, although the condition is said to have been described as long ago as the time of Hippocrates.[3] Ronchese[4] reported 3 cases in 1936, and found 27 other typical cases in the literature. Tobias[5] and Coe and Silvers[6] have also given excellent reports of cases and reviews of the literature.

The clinical features of cutis elastica are (1) hyperelastic skin, which can be stretched easily for from 2 to 10 inches (5 to 25 cm.) above the surrounding skin; (2) a tendency of the skin to split easily on slight trauma; (3) usually papyraceous scars resulting from these lacerations which occur more commonly on the knees and elbows; (4) subcutaneous nodules, hematomas and pseudotumors forming in the tissues as an after-effect of trauma, and (5) articular overrelaxation in almost every case. Other fairly common symptoms which are not essential to the diagnosis are vascular nevi, chilblains and acrocyanosis.

A number of different names have been applied to the syndrome; the ones most acceptable are cutis elastica and dermatorrhexis. Ronchese makes a strong case for the name dermatorrhexis with or without dermatochalasis and/or arthrochalasis. He considers dermator-

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From the Department of Pediatrics, the Fargo Clinic and the North Dakota Children's Program.

1. Ehlers, E.: Cutis laxa, Neigung zu Hoemorrhagien in der Haut, Lockerung meher Artikulationen, Dermat. Ztschr. **8**:173, 1901.

2. (*a*) Danlos, M.: Un cas de cutis laxa avec tumeurs par contusion chronique des coudes et des genoux (xanthome juvenile pseudo-diabetique de M. M. Hallopeau et Mace de Lepinary), Bull. Soc. franç. de dermat. et syph. **19**:70, 1908. (*b*) Pautrier, L.: Note histologique sur le cas de cutis elastica avec pseudo-tumeurs aux genoux et aux coudes, presente par M. Danlos, ibid. **19**:72, 1908.

3. Burrows, A.: Epidermolysis Bullosa with Cutis Hyperelastica, Proc. Roy. Soc. Med. **25**:1319, 1932.

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6. Coe, M., and Silvers, S. H.: Ehlers-Danlos Syndrome (Cutis Hyperelastica), Am. J. Dis. Child. **59**:129 (Jan.) 1940.

rhexis the most important part of the disease, indicating the fragility of the skin and tendency to split on slight trauma. The name cutis elastica calls attention to one of the more significant characteristics of the syndrome and has the advantage of being somewhat clearer and simpler than the name dermatorrhexis. To call the condition the Ehlers-Danlos syndrome, or the Danlos syndrome, has the drawbacks inherent in naming any disease after a person or persons. Other terms which have been used with some merit are cutis hyperelastica, cutis laxa and dermatolysis; the latter two names are now generally used to describe other diseases.[7]

The etiology is unknown. The disease is congenital, and it is noticed either at birth or by early childhood. In some cases it is apparently inherited as an incomplete dominant characteristic.[8] In the majority of cases there is no known hereditary factor. There is no association with mental defect. It occurs in both sexes. A relationship to von Recklinghausen's neurofibromatosis has been suggested.[9] Microscopic examination of skin and of nodules gives no clue as to pathogenesis. As a rule the corium shows some decrease in collagen, with an overabundance of loose connective and elastic tissue and thinning of all layers of the skin and subcutaneous tissue. The nodules are lipomatous.[10] In cases in which roentgen examinations were carried out the skeleton has been described as normal in structure and maturation, but scoliosis[11] and dislocation of patellas[1] and radiuses[8] have been described. In only a few cases have laboratory studies given abnormal results.[12] The cellular constituents of the blood and bleeding and clotting mechanisms are normal in almost every instance.

The diagnosis should not be difficult in the typical cases, but is not always easy in the modified types. In the newborn infant there is a condition known as cutis laxa[7] in which the skin is loose and wrinkled; in several months it corrects itself; the cause is unknown. Dermatolysis is a condition occurring in older subjects, in which the skin in certain locations becomes redundant and thickened, particularly on the face, neck and scalp. It is often associated with neurofibromatosis. The lesions are progressive and should be excised. Epidermolysis bullosa should cause no confusion, as it shows no tendency

7. Holt, L. E., and Howland, J.: Holt's Diseases of Infancy and Childhood, ed. 11, revised by L. E. Holt Jr. and R. McIntosh, New York, D. Appleton-Century Company, Inc., 1940, p. 851.

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9. Bielschowsky, F.: Beitrag zur Klinik und Pathologie der Lipatrophia circumscripta (Cutis laxa), Deutsches Arch. f. klin. Med. **166**:96, 1930.

10. (*a*) Tobias.[5] (*b*) Shaw, A. B., and Hopkins, P.: A Case of a Boy, Aged Seven, Showing (a) Double-Jointedness, (b) Dermatolysis ("Elastic Skin") with Great Friability of the Skin and Excessive Tendency to Bruising, and (c) Multiple Subcutaneous Tumours on the Limbs (Fibromata, Neuoromata), Proc. Roy. Soc. Med. (Clin. Sect.) **6**:20, 1913.

11. Margarot, Devese and Coll de Carrera.[8] Shaw.[10b]

12. (*a*) Tobias.[5] (*b*) Dreyfus, G.; Weill, J.; Martineau, J., and Mathivat, A.: Un cas de maladie d'Ehlers-Danlos, Bull. et. mém. Soc. méd. d. hôp. de Paris **52**:1463, 1936.

toward elastic skin, articular overrelaxation or formation of subcutaneous nodules. Also, the cutaneous lesions differ in appearance from those of cutis elastica.

There is no known treatment. Most of the cases in the literature are those of persons in whom the condition was mild enough to be compatible with normal activity.

REPORT OF CASES

CASE 1.—G. D. S. was born on June 12, 1944. Forceps were used. Weight at birth was 7 pounds 9 ounces (3,4303 Gm.). During the first twelve hours of life the baby was cyanotic and flaccid. The fingers were wrapped so tightly in the

Fig. 1. (G.D.S.)—*A*, overelasticity of skin and subcutaneous tissue of forearm; *B*, overlasticity of tissues of thigh; *C*, extreme laxity of skin and subcutaneous tissue of hand.

palm of the hands that it was impossible to unwrap and extend the fingers for several weeks. There was a cystlike growth in the midline of the alveolar process of the lower jaw measuring about 1 by 2 cm. in diameter; this was removed shortly after birth; it contained two teeth. The family history was noncontributory. There were no siblings. The mother had had no miscarriages. The mother's age was 24 years at the time of the baby's birth, and the father was 28 years old; both were in good health. There was no family history of cutis elastica or other congenital difficulties on either side of the family. There was no consanguinity. The mother's pregnancy was normal except for cramps and the passing of a few clots on Dec. 30 and 31, 1943. She had a well balanced diet, which included added iron and calcium for the last four months of pregnancy.

On July 18, the baby was seen by Dr. R. E. Dyson, pediatrician at Minot, N. D. The baby weighed 8 pounds 9 ounces (3,883.8 Gm.). The body length was 20½ inches (62 cm.), the circumference of the head was 15 inches (38.1 cm.), the circumference of the chest 12 inches (30.4 cm.) and the abdominal circumference 12½ inches (31.6 cm.). The hands were clenched tightly. The mandible was small and receding. There was a strawberry hemangioma on the upper part of the right side of the chest 0.2 inches (0.5 cm.) in width and 0.5 inches (1.27 cm.) in length; this was treated with radium. The extremities were lax and the joints hyperextensible. The right patella was lateral to the normal position. Craniotabes was present in the right parietal region, and the anterior and posterior fontanels were large. The lungs and heart were normal. The abdomen presented large epigastric and umbilical hernias; a left inguinal hernia was also present. The epigastric and umbilical hernias were kept strapped with adhesive tape; a yarn truss was used on the inguinal hernia. The baby was referred for consultation to an orthopedist who saw the patient on Aug. 24, 1944. He considered the case one of congenital dysplasia of an unusual variety. In addition to the other anomalies, dislocation of the hips was present on the basis of relaxation of the joints. He did not think it advisable to try reducing the hips at that time, but thought that it might be possible later.

I first saw the patient in the spring of 1945 at the age of 11 months. Because of the many unusual features of his case it was suggested that the baby be hospitalized for further study. He was admitted to St. Luke's Hospital on Aug. 23, 1945, at the age of 14½ months. His weight at that time was 17 pounds (7,711 Gm.). His temperature was 100 F. rectally. He presented findings typical of cutis elastica to a marked degree. His skin was smooth and soft, and in every portion of the trunk and extremities it could be lifted easily for from 2 to 6 inches (5 to 15 cm.) (fig. 1), and when released it snapped immediately back to perfect alinement with the surrounding skin. The same elasticity was noted in the skin of the face, particularly of the cheeks and to a less extent on the forehead, nose and chin. It was noted that slight trauma caused ecchymoses and hematomas to appear. The baby was unable to sit up or turn over. During the initial examinations and subsequently, the hands and feet kept up an athetoid motion almost continuously. The head was normal in size and shape; the anterior fontanel was large; the sutures were closed; there was no evidence of craniotabes. The eyes reacted well to light and in accommodation; they were alert and followed the movements of the examiner. The ear drums were gray and glistening. Three upper incisor teeth were present. The mandible was receding in type. The neck was flexible. The chest was clear to percussion and auscultation. The outline of cardiac dulness was not enlarged. There were no heart murmurs; heart rate and rhythm were normal. The abdomen was soft and rounded. The liver and spleen were not enlarged. There was a rather large umbilical hernia and an epigastric hernia in the midline. He had normal male genitals. All the joints of the body were extremely relaxed and hyperextensible (fig. 2). The right leg was slightly shorter than the left leg. The patellas could be displaced laterally with ease. There was left lumbordorsal scoliosis (fig. 3). The baby did not say any words, but made sounds indicating interest in his surrounding. He reached for and held objects extended to him.

Laboratory and roentgen studies were carried out. Reactions of the blood to the Kahn and Kolmer tests were negative. Serum calcium was 11.9 mg. per hundred cubic centimeters, phosphorus 3.7 mg. Serum cholesterol was 159 mg. and hemoglobin 13 Gm. per hundred cubic centimeters of blood; red blood cells numbered 4,590,000; white blood cells 11,450 and blood platelets 185,000 per cubic millimeter; bleeding time was one minute and fifteen seconds, coagulation time three minutes and thirty seconds. The urine was straw colored; specific gravity

was not determined because of insufficient quantity. There was no albumin and no sugar in the urine; the microscopic examination gave normal results. Roentgen examination showed the chest normal, except for bilateral rudimentary cervical ribs, and the skull with a widely open anterior frontanel. There was some asymmetry of the parietal cortex with moderate thickening on the right. Roentgen studies of the spine and long bones revealed dislocation of the right hip and possible

Fig. 2. (G.D.S.)—Relaxation and hyperextensibility of hip joint.

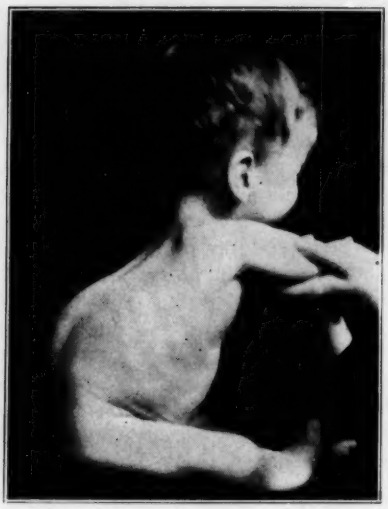


Fig. 3. (G.D.S.)—Note the presence of scoliosis.

dislocation of the left hip with poorly developed joint structures. There was scoliosis to the left of the lumbar and dorsal spine. Bone maturation and bone structure were normal for his age.

A biopsy specimen was taken of the skin from the anterior surface of the right thigh. It showed an excess of loose connective tissue and elastic tissue (fig. 4).

The baby was discharged from the hospital on Aug. 29, 1945. A letter was received from the mother in December, stating that two lower molar teeth had erupted and that there were signs of lower incisor teeth also. He was last seen in November 1946. At that time he was making excellent progress mentally. In some respects his physical progress was favorable also, as he was handling his spoon and cup well enough to eat alone. He was able to sit alone, but his scoliosis was a little more pronounced, requiring application of a corset-like support for his back. The physical findings were otherwise as before; no athetoid movements were present at that time.

CASE 2.—L. L. was born on May 1, 1938. Her birth weight was 5 pounds 6 ounces (2,438 Gm.). Birth was spontaneous and the neonatal condition was good.

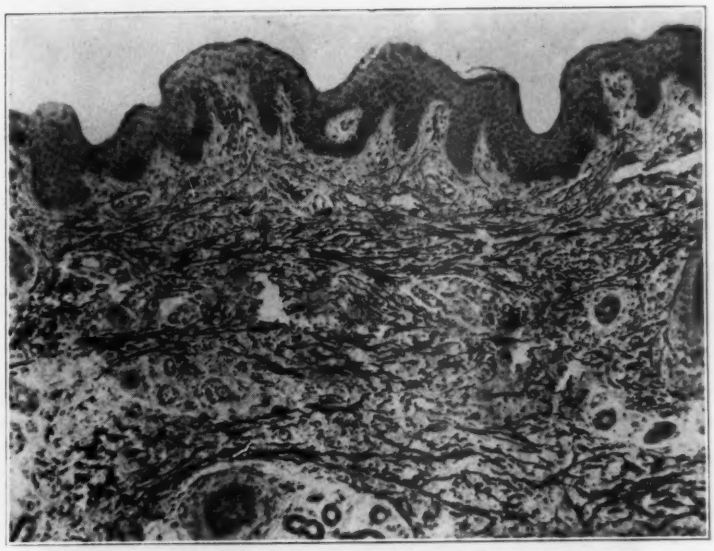


Fig. 4. (G.D.S.)—Biopsy specimen of skin showing excess of loose connective tissue and elastic tissue fibers.

The mother's pregnancy and labor were normal. The baby was vigorous and active. The general physical examination revealed a normal child except for epicanthic folds of both eyes. At 1 month of age she weighed 8 pounds 3 ounces (3,713.8 Gm.); at 7 months she weighed 16 pounds 6 ounces (7,427.5 Gm.) and was 25½ inches (64.7 cm.) in length. Immunizations were started at 4 months and completed at 10 months. At 10 months of age orthopedic consultation was obtained because of mild varus deformity of the forefeet. The orthopedic note stated that the feet were flaccid and could be manipulated easily. A progress note five months later stated that the feet were extremely flexible.

At 2 years of age the patient weighed 29 pounds 4 ounces (13,267.5 Gm.) and was 33 inches (83.82 cm.) tall. The blood hemoglobin was 66 per cent, and prescription for an iron preparation was given. Her feet were in fairly good condition; she was wearing corrective shoes. At 3½ years of age the first mention appears of irritation and swelling of the tissues overlying the first metatarsophalangeal joints. This was considered due to the construction of the shoes, in which changes were advised.

At 4 years of age the child was taken to a plastic surgeon who removed the epicanthic folds of both eyes. Rather deep scarring occurred at the operative sites (fig. 5).

I first saw the child in June 1946, when she was 8 years old. Physical examination showed her to be well developed and nourished and in good general health. There were rather deep operative scars near the inner canthi of the eyes. The skin showed numerous paper-like scars over both knees and tibias (fig. 6). Several ecchymoses were present on the anterior portions of the legs. There were a number of small firm subcutaneous nodules over the anterior part of the tibias. The skin of the extremities was slightly overelastic, stretching for from 1 to 2 inches (2.5 to 5 cm.) above the surrounding skin, and dropping quickly back into place when

Fig. 5. (L.L.)—Scarring at site of removal of epicanthic folds.

released. The skin had a velvety texture similar to that of the other child (G. D. S.). The feet showed reddening and thickening of the skin and subcutaneous tissue, most marked over the achilles tendons where the shoes had caused friction; there was a subcutaneous nodule on the left heel. The bony landmarks of the feet were prominent, and there was some thickening and reddening of the overlying skin and subcutaneous tissue. There was no flattening of the longitudinal arches, which were rather high. Both forefeet were unusually flexible and relaxed on manipulation; the toes were moderately hyperextensible. There was some tendency to toe in. The mother stated that the child had obtained considerable relief of foot discomfort from shoes with built in arch supports and lifts on the outer aspect of

both soles. The fingers of both hands were moderately hyperextensible. The skin and subcutaneous tissues of the hands and forearms had the velvety texture found in the lower extremities. There were no scars or subcutaneous nodules in the upper extremities.

A biopsy specimen was taken from the skin of the anterior surface of the right leg. This showed changes similar to those found in G.D.S., namely an excess of loose connective tissue and elastic tissue fibers in the skin and subcutaneous tissue.

Laboratory and roentgen findings were essentially normal. Roentgen examination showed normal bone structure of the lower extremities and a normal chest. Red blood cells numbered 4,050,000 per cubic millimeter with a hemoglobin of 12

Fig. 6. (L.L.)—Knees and tibias showing papyraceous scars.

Gm. White blood cells numbered 8,750, with lymphocytes 63, polymorphonuclear leukocytes 31, and eosinophils 6. The sedimentation rate was 6 mm. in one hour. The blood urea was 42.1 mg. per hundred cubic centimeters and the blood urea nitrogen 19.6 mg. Serum cholesterol was 190 mg. per hundred cubic centimeters and serum protein 5 Gm. The urine was acid, *p*H 5.5, and albumin was present (1 plus) but was absent when the test was repeated later; there was no sugar; microscopic examination gave normal results except for calcium oxalate crystals. The mother's

blood had given negative reactions to tests for syphilis prior to the birth of the patient.

The family history was entirely normal. The mother, father and one sibling were in good health. There was no consanguinity and no history of any congenital defects on either side of the family.

The child was last seen in January 1947, and was getting along well. There continued to be mild discomfort of the feet at times, which had been aggravated recently by ice skating.

COMMENT

These 2 cases illustrate the wide variation possible in cutis elastica. In case 1 the patient has involvement as extensive as any reported. His articular relaxation is particularly severe, and the presence of dislocated hips, severe scoliosis and a tendency toward dislocation of other joints makes the outlook unfavorable for standing and walking unless ligaments and tendons show spontaneous improvement in tone. In case 2, on the other hand, the child's articular relaxation is mild and is present only in the feet and in the metacarpophalangeal joints of the hand. Examples in the literature of the mild[13] and the severe types[14] emphasize the possible differences.

In both of my cases the skin has the smooth velvety texture characteristic of the disease. When picked up between thumb and forefinger it gives a sensation as though gliding over a well oiled surface. When released the skin slides back quickly to its original position, leaving no sign of having been disturbed. The amount of hyperelasticity was much different in the 2 cases, being generalized and pronounced in the child in the first case, while being slight and confined chiefly to the extremities in the other patient. In some of the other cases reported this tendency has also been localized, usually in the region of the knees and ankles.[15]

The fragility of the skin, with a tendency to split and form scars on slight trauma, is reportedly present in all cases. It is most evident in areas subject to the greatest trauma such as the knees, shins and elbows and sometimes even the chin and forehead. The scars are thin and papyraceous, and are well illustrated in our second case (fig. 6). In this child there is scarring over the knees and anterior tibial surfaces. There is also a scar adjacent to the inner canthus of both eyes

13. (*a*) Tobias.[5] (*b*) Gilbert, A.; Villaret, M., and Bosviel, G.: Sur un cas d'hyperelasticite congônitale des ligaments articularies et de la peau, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:303, 1925. (*c*) Weber, F. P.: The Ehlers-Danlos Syndrome, Brit. J. Dermat. **48**:609, 1936. (*d*) Schulmann, E., and Levy-Coblentz, G.: Hyperelasticite cutanée (cutis laxa) et laxite articulaire avec fragilite anormale de la peau et tumeurs molluscoides post-traumatiques (syndrome de Danlos), Bull. Soc. franç. de dermat. et syph. **39**:1252, 1932.

14. Ehlers.[1] Coe and Silvers.[6] Margarot, Devese and Coll de Carrera.[8] Shaw.[10b] Dreyfus, Weill, Martineau and Mathivat.[12b] Brain, R. T.: Dermatolysis and Fragility of the Skin, Proc. Roy. Soc. Med. **29**:923, 1936.

15. Tobias.[5] Weber.[13c] Poynton, F. J., and Paterson, D.: Congenital Deficiency of the Subcutaneous Fibrous Tissue Associated with Nodules Due to Dilated Arterioles, Proc. Roy. Soc. Med. **14**:7, 1921. Langmead, F.: Case of Calcinosis, ibid. (Clin. Sect.) **16**:23, 1923.

(fig. 5), where surgical treatment was carried out to remove epicanthic folds. Subcutaneous nodules, another common feature of the disease, are present over both shins and on one heel. There are no such nodules in the case of the first child, and no scarring, probably because of his relative inactivity. These nodules are thought to be late effects of trauma. The first child bruises easily, however, and is prone to get ecchymoses if not handed with unusual gentleness. This tendency is not a prominent feature in the other child.

SUMMARY

Two cases of children with cutis elastica are represented, showing the clinical features and variations which may occur. There is no known therapy.

SYMPOSIUM ON ENCEPHALOPATHIES

WHAT TYPES OF EPILEPTIFORM-LIKE SEIZURES ARE AMENABLE TO SURGICAL TREATMENT?

Surgical Treatment of Epilepsy Due to Atrophic Cerebral Lesions

T. C. ERICKSON, M.D.
MADISON, WIS.

THE TERM epileptiform-like seizures contained in my title is not to my liking, for it carries a double implication that there are seizures like epilepsy which are not true epilepsy. This concept of true, essential or idiopathic types of epilepsy obscures the facts. Epileptic seizures are a symptom of some abnormal condition affecting the central nervous system and causing an excessive and abnormal neuronal discharge, the type of seizure depending on the particular portion, or portions, of the brain involved. Although more than sixty "causes" of epilepsy have been described, it is often impossible to determine the actual cause, and one is then forced to speak of idiopathic or, better, cryptogenic epilepsy. The number of patients with the latter type will no doubt become fewer as knowledge increases.

For the purpose of the present discussion, patients with epilepsy may be placed in two general groups: those with and those without demonstrable cerebral lesions (table 1). It is for the patients in the first group with cerebral neoplasms, abscesses or cicatrices that surgical treatment may be indicated. Since Dr. Putnam will discuss the problems posed by patients with tumors, I shall confine my discussion largely to the management of those with atrophic lesions. It should be noted, however, that the distinction between these two conditions is not always apparent in early stages of study of the patient.

When one is faced in practice with a child having seizures, it is not always possible to make an etiologic diagnosis without an extensive investigation. A presumptive diagnosis often may be made, however, by a consideration of the commonest causes of epilepsy in children of various age groups as presented in the following table (table 2). Such a presumptive diagnosis is of great help in directing further

This paper and the six which follow it were presented at the Symposium on Encephalopathies at the meeting of the American Academy of Pediatrics, Hotel William Penn, Pittsburgh, Wednesday, Feb. 26, 1947.

TABLE 1.—*Etiologic Classification of the Epilepsies**

A. With demonstrable cerebral lesions		Produced by
Atrophic cerebral lesions	1. Expanding lesions	Neoplasm, abscess
	2. Cerebral cicatrix	Trauma, infection
	3. Local cerebral atrophy	Compression, ischemia, infection
	4. Local cicrogyria	Infantile compression or ischemia
	5. Cyst of the brain	Vessel closure or hemorrhage
	6. Diffuse cerebral disease	Degeneration, infection, sclerosis
	7. Diffuse cerebral vascular disease	Arteriosclerosis, syphilis
	8. Miscellaneous	Congenital lesions
B. Without demonstrable cerebral lesions		Produced by
	1. Cryptogenic (idiopathic)	Abnormal cerebral physiologic function
	2. Toxic and febrile	Extracerebral causes
	3. Hypoglycemic	Extracerebral causes
	4. Miscellaneous (angioneurotic, circulatory arrest)	

*This table is taken from Penfield and Erickson.[2]

clinical inquiry. Careful and thorough study of all epileptic patients is a necessary prerequisite to surgical treatment. The methods of studying these patients may be divided into clinical, roentgenologic and electroencephalographic procedures.

TABLE 2.—*Presumptive Differential Diagnosis Based on Age of Onset*

Age of Onset		Presumptive Cause
Period	Years	
Infancy	0 to 2	Birth trauma, tetany, febrile illness, congenital or degenerative disease
Childhood	2 to 10	Birth injury, febrile cerebral thrombosis, cerebral trauma, cryptogenic orgin
Adolescence	10 to 20	Cryptogenic origin, cerebral trauma
Youth	20 to 35	Trauma, neoplasm, cryptogenic origin
Middle age	35 to 55	Neoplasm, trauma, arteriosclerosis
Senescence	55 to 70	Arteriosclerosis, neoplasm

In taking the history of the patient with epilepsy several points are of prime importance in making a decision whether surgical treatment is indicated.

Do the seizures have an onset indicating a focal cerebral lesion? Description of the seizures should be obtained not only from the pa-

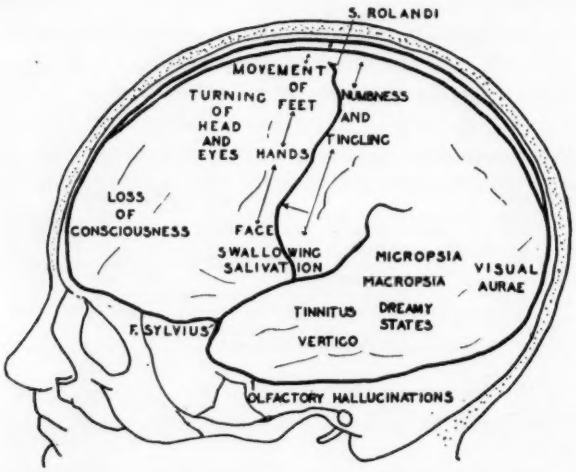
TABLE 3.—*Clinical and Anatomic Classification of Epileptic Seizures**

Clinical Type	Localization
Motor	
1. Generalized seizure (grand mal)	Motor and associated systems
2. Jacksonian seizure (focal motor, partial)	Prerolandic gyrus
3. Masticatory (smacking, salivation, swallowing)	Lower rolandic gyrus
4. Simple adversive seizure	Frontal, premotor areas
5. Tonic seizure ("cerebellar," decerebrate)	Brain stem
Sensory (auras)	
6. Somatosensory seizure	Postrolandic gyrus
7. Visual seizure (lights, darkness)	Occipital and postparietal region
8. Auditory seizure (buzzing)	Temporal region
9. Vertiginous seizure (dizzy spell)	Temporal region
10. Olfactory seizure (uncinate)	Infratemporal area
Visceral	
11. Autonomic seizure (vasovagal)	Diencephalic region
Psychic	
12. Petit mal seizure (lapse, absence, pyknolepsy)	
13. Psychomotor seizure (confusion, coordinated misbehavior)	
14. Automatism, postepileptic confusion	
15. Dreamy state (deja vu, unreality, near, remote	Temporal region
16. Psychotic states (secondary)	

*This table is a modification of one presented by Penfield and Erickson.[2]

tient but also from parents or relatives who have observed the attacks. Inquiry concerning the aura or the onset of the attack should be speci-

fic and detailed. A full description of the seizure and of any postictal paralysis should be recorded. It was pointed out by John Hughlings Jackson that epilepsy begins as an excessive, local neuronal discharge which spreads by contiguity to adjoining areas of the cortex. When this site of origin is in the subcortex or the frontal lobe, the entire cerebral cortex may be involved simultaneously, so that the attack appears to be a generalized process from the onset. However, when the character of the seizures and their onset is known, one can usually localize the site of the epileptogenic lesion from a knowledge of cerebral localization (figure).



Cerebral localization as indicated by onset of epileptic seizures.

Turning of the head and the eyes to the opposite side (an adversant seizure) is one of the commonest modes of onset of an epileptic seizure, and it usually indicates an epileptogenic lesion in the premotor area. The fact that a lesion irritating the precentral gyrus produces a typical jacksonian march is well known. Scarff[1] described a particular group of children in whom seizures begin in the foot, which may be relieved by lysis of pacchionian granulations. Attacks which have their onset with numbness or tingling of the arm or leg indicate a lesion of the postcentral gyrus, and those which begin with dizziness or with a buzzing indicate a lesion of the temporal lobe. A lesion low enough in the temporal region to affect the uncinate gyrus produces an olfactory hallucination, usually an unpleasant odor. A further discussion of the problem of localization is outside the scope of this paper. (For a more complete discussion of the subject of cere-

1. Scarff, J. E.: A Specific Epileptic Syndrome Relieved by Lysis of the Pacchionian Granulations: Preliminary Report of Three Cases, Arch.. Neurol. & Psychiat. **36**:373-374 (Aug.) 1936.

bral localization, the reader may refer to any good textbook of neurology or to the study by Penfield and Erickson.[2])

The next question to be asked of the epileptic patient or his parents concerns a possible cause for focal pathologic changes in the brain. Does the patient have a history of head injury, difficult or prolonged birth, old abscess of the brain, meningitis or cerebral venous thrombosis which may have been responsible for the development of a focal contracting cerebral lesion?

Examination of the patient may provide evidence of the presence of a focal cerebral lesion. An old scar on the scalp or a defect in the bone may indicate the site of a meningocerebral cicatrix following a severe head injury, such as occurs from a forceps delivery. Asymmetry of the skull may be evident either on clinical examination or on the roentgenograms, and, if it appears, it indicates the presence of an atrophic lesion dating from childhood. Bodily asymmetry also may result from a destruction of portions of the parietal lobe, so that it is a valuable localizing sign. The symmetry of the two sides of the body must be carefully examined by measuring the distance of the nipples from the midline of the body and by comparing the size of the hands, arms and legs on the two sides. Such bodily asymmetry may be evidence of a destructive lesion in the postcentral region.

The results of neurologic examination are of prime importance, for they may provide a clue to the location of a focal lesion when no other evidence is present. However, the neurologic examination may reveal no abnormality, even in the presence of a large cicatrix. In such patients examination immediately after a seizure may disclose localizing signs. Reflex changes or paralysis may be present for a few minutes, hours or even days after a severe epileptic seizure. Such postictal paralysis may furnish signs of localization when other evidence is lacking.

When no adequate description of the seizures is available, it is advisable to have the patient admitted to a hospital where the attacks can be objectively observed and described by trained nurses and house officers. The first step is to discontinue all anticonvulsant medication. Not infrequently, patients who have been receiving phenobarbital go into status epilepticus when their medication is suddenly discontinued; for this reason they should be carefully watched, and the medication should be reinstituted as soon as a seizure has been adequately described. If no attack occurs with cessation of medication, some method must be employed to precipitate the attacks. The simplest

2. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941.

of these procedures is the hyperventilation test, which is, however, effective in only 10 to 15 per cent of patients. The patient is made to breathe as deeply and as rapidly as possible for ten minutes. When cooperation is good, carpopedal spasm and a positive Chvostek sign appear in two to three minutes, and in susceptible patients a typical seizure follows. Pentamethylenetetrazol ("metrazol") injection has also been used for the purpose of precipitating a typical seizure while the electroencephalogram is being taken.

A reliable and useful means of precipitating an attack is the hydration regimen suggested by McQuarrie and Peeler.[3]

1. Give water by mouth, 3 to 5 cc. per kilogram of body weight per hour (this may be flavored with lemon juice and sugar).
2. Weigh patient every six hours after he has voided (expect from 2 to 6 per cent gain in weight).
3. Measure and chart patient's intake and output.
4. Administer betahypophamine ("pitressin") intramuscularly, 0.5 cc. every three hours, increasing the dose gradually to 1.5 cc.
5. Observe and record carefully all symptoms, such as headache, nausea, vomiting, dizziness, drowsiness and malaise, as well as convulsions.
6. Discontinue this regimen as soon as two convulsions have been observed from the onset and accurately described.
7. Immediately recommence anticonvulsant medication, such as phenobarbital, so as to prevent the patient's going into status epilepticus.

When focal epileptiform seizures have been accurately seen or described, it is desirable to proceed with roentgenologic and electroencephalographic studies. To save time, one may better carry them out simultaneously.

Stereoscopic lateral and anteroposterior roentgenograms of the skull should be made for all epileptic patients. The presence of an old, depressed fracture or of fracture lines in the skull may indicate the site of a meningocerebral cicatrix. Defects in the skull as the result of old head injuries or of the drainage of healed abscesses of the brain may be disclosed. "Stalactite" formation from the internal surface of the skull may occur, if there has been a defect in the dura. An asymmetry of the two sides of the skull may indicate the presence of an atrophic cerebral lesion on the smaller side, dating from early childhood. Such disorders are some of the common observations in the presence of epilepsy due to an atrophic cerebral lesion. Clinically, the dividing line between expanding and contracting, or atrophic, cerebral lesions as the cause of seizures may not be evident on preliminary examination; roentgenograms of the skull may disclose evidence of a slowly growing neoplasm as the cause of the seizures. However,

3. McQuarrie, I., and Peeler, D. B.: The Effects of Sustained Pituitary Antidiuresis and Forced Water Drinking in Epileptic Children: A Diagnostic and Etiologic Study, J. Clin. Investigation **10**:915-940, 1931.

a normal roentgenogram of the skull does not rule out the presence of a cerebral cicatrix.

Pneumoencephalography is one of the most valuable diagnostic aids to reaching a decision as to the advisability of operative intervention in a patient with epilepsy. Local dilatation, or tenting, of the outlines of the ventricles, displacement of the septum pellucidum toward the side of the lesion and abnormal collections of gas, porencephalia and uneven filling of the subarachnoid space are the important indications for operation. These roentgenographic signs should be evaluated in the light of the localization of the epileptogenic lesion made from neurologic examination and from study of the patient's seizures. Valuable confirmation may be furnished by the electroencephalogram.

Electroencephalographic studies of the epileptic patient give evidence which, when combined with the results of clinical and pneumoencephalographic studies, enables one to make a proper choice of the patients who are suitable for operative treatment. If the electroencephalographic focus corresponds with the clinical and roentgenologic localization, there is good reason for surgical intervention. Electroencephalography is especially valuable as a preliminary test in the office or dispensary to decide whether further study of the patient in the hospital is advisable. Reviews of the clinical applications of electroencephalography may be found in the monograph by Gibbs and Gibbs[4] and in the chapter by Jasper in the study by Penfield and Erickson.[2]

INDICATIONS FOR OPERATION

In cases of focal epilepsy, the decision whether operation should be undertaken depends, then, on the presence of positive evidence of a focal cerebral lesion, as judged by the clinical evidence and as confirmed by the results of pneumoencephalographic and electroencephalographic studies. Surgical treatment should not be undertaken for an atrophic lesion unless the evidence from at least two, and preferably three, sources agrees closely. A period of trial with medical therapy is almost always advisable, if the presence of an expanding lesion has been ruled out. The contraindications to operation are, first, the absence of objective evidence of a focal lesion and, second, the presence of diffuse or multiple lesions. In nonfocal epilepsy, surgical therapy has little justification unless there is evidence of increased intracranial pressure, such as occurs not only with brain tumors but also with craniostenosis. In the latter condition, subtemporal decompression may be indicated. Decompressive operations are of no value in

4. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Boston, The Authors, 1941.

the treatment of epilepsy unless increased intracranial pressure is specifically indicated. The presence of multiple lesions is not an absolute contraindication; for in a few instances multiple, but discrete, cerebral cicatrices have been removed wtih subsequent cure of the epilepsy. In most cases, however, multiple cicatrices cannot be removed with benefit to the patient. Although the presence of advanced mental deterioration does not augur well for the results of the operation, lesser degrees of personality change may be improved.

The excision of cerebral and meningocerebral cicatrices was shown to be successful insofar as the cerebral lesion, or lesions, could be located and completely removed. In a series of 154 patients operated on by Penfield who were carefully traced for periods ranging from one to ten years after operation,[2] the following results were observed. With excision of a meningocerebral cicatrix, 45 per cent of the patients showed a decided improvement and an additional 32 per cent a moderate improvement, making a total of 77 per cent who were considered to show a definite improvement. With excision of a cerebral cicatrix, 40 per cent of the patients were definitely improved, while an additional 19 per cent were moderately improved, making a total of 63 per cent with a worth while improvement.

A control group, consisting of patients in whom a craniotomy was performed but in whom no significant focal lesion was found, showed a pronounced improvement in only 5 per cent of the patients. The results obtained in this group of negative explorations proved three things: first, that a simple craniotomy, even when accompanied with decompression, does not produce improvement; second, that the improvement in the first two groups was due to the excision of the lesion and was not due to altered or improved medical treatment, for all three groups were treated similarly in this respect; and, third, that the incidence of spontaneous remission in this type of epilepsy is 5 per cent or less. The operative mortality in the entire series was 4 per cent, and 2 per cent of the patients considered that they were worse after operation.

The removal of cerebral neoplasms or expanding lesions in patients with epileptiform seizures results in a "cure" of seizures in about the same percentage of patients as are cured by excision of cerebral cicatrices (Penfield, Erickson and Taylor).[5] If the seizures continue after operation, one must suspect a recurrence of the neoplasm or the formation of a cicatrix. The same developments must be suspected when the seizures occur for the first time after operation for removal of an expanding lesion.

5. Penfield, W.; Erickson, T. C., and Tarlov, I.: Relation of Intracranial Tumors and Symptomatic Epilepsy, Arch. Neurol. & Psychiat. **44**:300-315 (Aug.) 1940.

What factors influence the prognosis following surgical excision of cerebral and meningocerebral cicatrices? Age has no demonstrable effect on the ultimate result of operation for excision of the meningocerebral cicatrices. The location of the cicatrix appears to have a definite effect on the results of excision. Those cicatrices in the frontal lobe, for example, which can be adequately excised without danger of involving the motor area have a better prognosis than those in the parietal region. The duration of attacks preoperatively has no demonstrable effect on the prognosis following excision of a meningocerebral cicatrix. Two cases illustrate this statement. One patient who had had severe, frequent seizures for seventeen years prior to excision of a meningocerebral cicatrix of the frontal lobe has been entirely free from fits during the five years which have elapsed since his operation. Another patient of similar age who had had fits for only six months prior to operation showed absolutely no change after surgical treatment; however, the excision was not a satisfactory one.

The frequency and severity of seizures have no apparent effect on the outcome of excision of the cicatrix. These observations are not necessarily incompatible with the view that such seizures leave their trace in the brain. The changes secondary to the fits which occur in the hippocampus and cerebellum[6] are not directly concerned with the pathogenesis of the epileptic seizures, while those progressive changes in the cicatrix and its neighborhood, as described by Penfield and Humphreys,[7] are local; hence they will be relieved by surgical excision.

If, however, there are severe mental changes associated with the epilepsy, the chance for alleviation of the fits seems definitely lessened, unless the lesion is absolutely localized. Patients with mental changes and meningocerebral scars have a better prognosis for relief of both the mental disturbance and the fits than those patients with cerebral atrophy or cerebral cicatrices.

When no gross pathologic change can be demonstrated by the usual thorough clinical investigations, combined with the special technics of pneumoencephalography and electroencephalography, the patient may be said to have cryptogenic (idiopathic) epilepsy. For this condition, a variety of surgical procedures, such as radical colectomy, oophorectomy and adrenalectomy, have been widely practiced in the past, and in the treatment of epilepsy they have been found worthless. Operations for the removal of a focus of infection have

6. Spielmeyer, W.: Die Pathogenese des epileptischen Krampfes, Ztschr. f. d. ges. Neurol. u. Psychiat. **109**:501-520, 1927.

7. Penfield, W., and Humphreys, S.: Epileptogenic Lesions of the Brain: Histologic Study, Arch. Neurol. & Psychiat. **43**:240-261 (Feb.) 1940.

rarely influenced the seizures. Such procedures are justified only when the existence of a focus of infection can be definitely proved.

Sympathetic ganglionectomy has been tried repeatedly as a cure for cryptogenic epilepsy. The period of trial has been sufficiently long to justify the conclusion that sympathectomy is a failure, unless there is a demonstrable abnormality of the sympathetic nervous system. Carotid sinuneurectomy has also been carried out in several series of patients with cryptogenic epilepsy, but without demonstrable benefit. It is to be recommended only when there is a definite abnormality of the carotid sinus mechanism.

Encephalography with oxygen or air results in the cessation of seizures in a small percentage of patients. The good results are almost all obtained in children under the age of 16 years. Subtemporal decompression has been tried by numerous surgeons; but there is no benefit to be derived from the procedure unless the seizures are secondary to a subdural effusion or are associated with a craniostenosis.

1300 University Avenue.

DIAGNOSIS OF BRAIN TUMOR IN CHILDREN

TRACY J. PUTNAM, M.D.
BEVERLY HILLS, CALIF.

TUMORS of the brain, while less common in children than in adults, are among the commonest tumors of childhood. Attention was first called to their peculiarities by Cushing[1], in a memorable paper entitled "The Intracranial Tumors of Preadolescence," in 1927. With Bailey, he established most of the diagnostic categories recognized today, and later work has added little to the masterly accounts of each type as given by him and his pupils. The subject has recently been restudied in a valuable book by Bailey, Buchanan and Bucy[2] entitled "Intracranial Tumors of Infancy and Childhood." I must acknowledge my indebtedness to both these sources.

While brain tumors include many pathologic types and are found in diverse locations, certain groups of symptoms are encountered in the majority of cases. Tumors of the brain are by definition expanding lesions, and, sooner or later, most of them produce an increase in the intracranial pressure, either by the addition of their own bulk to the cranial contents or by obstruction of the circulation of spinal fluid. The picture resulting from increased intracranial pressure in children is somewhat different from that seen in adults. Headache is somewhat rarer among children than among adults, but it is more significant because headache from other causes is so unusual in children. The location of the headache is of small significance, for pain produced by irritation of the great sinuses may be referred to the forehead or to the neck, or both, almost irrespective of the site of the lesion.

Vomiting is also a common symptom of brain tumor. Despite current teachings, the vomiting often is not projectile. It may or may not be accompanied with nausea, rarely with abdominal pain. In many patients the appetite is good, and the child can eat and retain a good meal immediately after vomiting has occurred.

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1. Cushing, H.: Intracranial Tumors of Preadolescence, Am. J. Dis. Child. **33**:551 (April) 1927.

2. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

Of the objective signs of intracranial tumor in children, the most important are those due to separation of the sutures. Bulging of the fontanels is obvious in infants, and, up to the time of closure of the sutures, a characteristic cracked-pot sound may be elicited on percussion of the head—Macewen's sign. This maneuver should be a part of every physical examination. More positive evidence of a separation of sutures is afforded by stereoscopic roentgenograms of the skull, which may also show atrophy of the sella turcica. The more specific localizing signs demonstrated by roentgenograms will be mentioned later.

Changes in the optic disks are, on the whole, rarer in children than in adults, in part perhaps because of the plasticity of the skull. The changes are observed in the majority of patients, however. In general, frank choking of the disk is seen in acute cases, oftenest as a result of a tumor obstructing the circulation of the spinal fluid. Secondary atrophy occurs early, and in many cases simulates exactly primary atrophy as seen in adults.

Increase in pressure often gives rise to a paralysis of the sixth nerve as it passes through the incisura of the tentorium. This paralysis is often mistaken for a focal sign of a lesion compressing the sixth nerve. If the peduncles herniate through the incisura, oculomotor palsies and vegetative disturbances may appear and signify a bad prognosis. The manifestations which I have described are all signs of increased pressure and are not, of course, diagnostic evidence of tumor. They also may be seen in cases of infantile hydrocephalus, subdural hematoma, lead poisoning and other conditions which will be considered later.

A slow, relentless progression of symptoms is well recognized as a characteristic manifestation of neoplasms in general. There are exceptions to the rule, however. The manifestations of tumors of the brain in children may be surprisingly remittent. They may, for example, appear only after an accident or illness, then disappear as the condition improves. Hospitalization is frequently followed by a minor remission. This curious circumstance does not, of course, alter the ultimate prognosis.

LOCALIZATION OF TUMORS

For purposes of diagnosis, it is convenient to classify tumors according to their location. Not only do the symptoms depend on the site of the tumor but also the histologic type of the growth may be inferred from its location.

The majority of the tumors seen in children are situated in the posterior fossa. Growths in this region in turn may be divided into three main groups: the tumors of the hemispheres, which are mostly

benign astrocytomatous cysts; the tumors of the fourth ventricle, which are mostly malignant medulloblastomas and ependymomas, and the tumors of the brain stem itself, which are practically all inoperable polar spongioblastomas.

Supratentorial tumors include those affecting the hemispheres, mainly gliomas of various types, with a few meningiomas and angiomas; the pineal group, chiefly pinealomas and teratomas; the suprasellar craniopharyngiomas, and the gliomas of the optic nerve.

SPECIFIC SYNDROMES

Cystic Astrocytomas of the Cerebellar Hemispheres.—This type is the commonest and most important tumor of childhood, of especial importance because, almost alone among the tumors of the posterior fossa, it is susceptible of being completely cured by surgical treatment.

Astrocytomas are slow growing. In the cerebellum, they gradually produce an obstruction to the circulation of spinal fluid and give rise to the signs of increased pressure. This mild, long-continued increase in pressure is particularly prone to cause atrophy of the sella turcica. Often the local signs are more striking than the signs of generally increased pressure. They include, of course, manifestations of the loss of cerebellar substance, appearing oftenest as adiadokokinesis, intention tremor and hypotonia, so that the hand can be hyperextended on the wrist or the forearm bent beyond a straight line at the elbow. A "forced" position of the head is common, the head being held at the angle which gives the tumor the most space inside the skull. Attempts to move the head into other positions cause pain and spasm of the neck.

As these tumors are slow growing, atrophy of the sella, separation of the sutures and a palsy of the sixth nerves are frequently seen. Direct involvement of the cranial nerves is relatively uncommon. A similar picture is produced by the hemangiomas of the cerebellum, which often are hereditary and accompanied with angiomas of the retina.

Medulloblastomas and Ependymomas of the Fourth Ventricle.—Both these structures are soft, rapidly growing, invasive tumors, usually springing from the floor or walls of the fourth ventricle. They are particularly common in children between the ages of 3 and 6 and occur oftener in boys than in girls. They quickly produce an increase in intracranial pressure, with early vomiting and ataxia beginning often before the sutures open or the disks become frankly choked. The diagnosis of digestive disturbance is often made. Palsies of cranial nerves are common.

These tumors are impossible to extirpate. Incision into the tumor often produces metastases throughout the spinal fluid pathways. Decompression, followed by deep radiation, gives a few years' relief in cases of medulloblastoma.

Lumbar puncture in cases of cerebellar glioma reveals a high initial pressure. Normal protein values and cell counts are obtained in the presence of gliomas; an increase in the protein level or a color change in the colloidal gold solution is suggestive of an angioma or of the rare neurinoma of the cranial nerves. Electroencephalography often discloses changes in pattern and phase reversal over the occipital lobes.

Gliomas of the Brain Stem.—These growths are slow growing, infiltrative lesions, which increase the intracranial pressure only late in their course. The earliest symptoms are usually various palsies of the cranial nerves, sometimes with unilateral or bilateral spasticity or sensory changes. The diagnosis of "encephalitis" is often suggested and may appear to be confirmed by the results of lumbar puncture, which often show no increase in intracranial pressure but an increase in the protein level and number of lymphocytes.

Tumors of the Hemispheres.—The majority of these lesions are of mesodermal origin, resembling sarcomas more than the meningiomas seen in adults. Next in frequency comes the ependymoma, a malignant glioma. Other gliomatous tumors also occur.

The tumors of the hemispheres produce seizures, hemiparesis, aphasia, hemianopsia and other focal symptoms, usually with a late increase in intracranial pressure. The localization can often be made by electroencephalographic studies. Lumbar puncture yields fluid under high pressure, usually with normal protein levels and cell counts. The amount of protein and even the quantity of cells may be increased, however, in persons with mesodermal tumors or those involving the floor of the ventricle. A color change in the gold solution is particularly common with meningeal tumors.

Craniopharyngiomas.—The tumors springing from Rathke's duct and pouch spread about the base of the brain, surrounding the optic nerves and the great vessels. Many of them are cystic, invading usually the temporal or frontal lobes. They produce optic atrophy, with blindness or hemianopsia, and often focal palsies or seizures. They may grow upward into the third ventricle, producing an acute hydrocephalus, or downward into the sella, causing atrophy of the hypophysis, with disturbances in growth and in the vegetative functions. Roentgenograms often show enlargement or atrophy of the sella and cloudy or shell-like calcification in the tumor. These lesions cannot be extirpated and are not affected by radiation. Sometimes the cystic growths may be drained into one ventricle.

Pinealomas.—A variety of tumors, most of them invasive, may spring from the pineal body. They characteristically produce the inability to turn the eyeballs upward, as a result of involvement of the superior colliculi. As they grow larger, pinealomas almost always obstruct the aqueduct and cause hydrocephalus. A certain amount of ataxia may occur, especially a tendency to fall backward. Precocious puberty is rare and is seen only in boys. Surgically, the prognosis is poor. The tumors are rarely sensitive to radiation.

A great variety of miscellaneous and atypical tumors occur in childhood, including adenomas of the hypophysis, gliomas of the optic nerve, angiomas, teratomas, chordomas and the like. Tubercles and gummas are now extremely rare. Limitations of space forbid a close examination of them.

SPECIAL DIAGNOSTIC METHODS

Electroencephalography.—The use of electroencephalography is of particular value in the differential diagnosis of idiopathic seizures from seizures due to tumors. Localization of surface lesions of the hemispheres is often possible; suggestive changes over the occipital lobes sometimes occur in the presence of large tumors of the cerebellar hemispheres or of the pineal gland. Electroencephalography can be employed only with cooperative children.

Lumbar Puncture.—The dangers of lumbar puncture in cases of brain tumor doubtless have been exaggerated. The procedure should probably be avoided when there are evidences of obviously increased intracranial pressure, but it is of greatest usefulness when the diagnosis of tumor is in doubt. When the lumbar puncture is performed on young children, a hypnotic dose of one of the more rapidly acting barbiturates should be given to permit a measurement of the basal pressure. If this pressure is more than 190 millimeters, an expanding lesion or an irritation of the meninges is probably present. An increase in protein content or a color change in the gold solution is suggestive of a mesodermal tumor, but either of these variations is occasionally seen with tumors affecting the lining of the ventricles. Tumors may produce softenings, which release showers of lymphocytes.

Encephalography and Ventriculography.—Injection of air by the lumbar route is a valuable means of differential diagnosis when the presence of a tumor is in real doubt. When a definitely increased intracranial pressure is present, ventriculography immediately followed by operation is probably more conservative. This procedure is often carried out in cases of brain tumor in children because of the relative difficulty in precise localization by clinical means.

416 Bedford Drive.

ELECTROENCEPHALOGRAM IN EPILEPSY

MEYER A. PERLSTEIN, M.D.
CHICAGO

ELECTROENCEPHALOGRAPHY, which has been in general use little more than ten years, finds its most popular employment in the study of convulsive disorders. The first direct study of the electric component of the activity of the brain was conducted by Hans Berger, who made recordings from the brains of animals in 1902 and from the human brain in 1924.[1] In the ten years that followed he succeeded in demonstrating most of the basic principles of electroencephography known today. In 1933, Fischer described the grand mal type of discharge as it appeared in animals treated with convulsant drugs.[2] The conception of epilepsy in human beings as a "paroxysmal cerebral dysrhythmia" was suggested by Gibbs, Gibbs and Lennox in 1937.[3] While never proposed as a substitute for careful clinical evaluation, electroencephalography, with accumulated observations and experience, has permitted an objective and more accurate differentiation of the convulsive disorders as to clinical manifestations, etiologic factors, prognosis and, in some cases, an evaluation of the effect of therapeutic measures. That it has been of invaluable assistance in the localization of organic lesions causing convulsions is, of course, generally recognized and conceded.

This paper does not profess to comprise an original contribution, being merely a summary of important facts about electroencephalography as it relates to epilepsy, particularly in children. The concepts described are almost entirely those of Gibbs and his colleagues, who have made major contributions to the use and interpretation of the technic in this country.

A brief, preliminary orientation seems in order. The cerebral cortex, like all other living tissue, exhibits electric activity which, more peculiar to this particular organ, is characterized by regular

1. Berger, H.: Ueber das Elektrenkephalogramm des Menschen: I. Mitteilung, Arch. f. Psychiat. **85**:527-570, 1929.

2. Fischer, M. H.: Elektrobiologische Auswirkungen von Krampfgiften am Zentralnervensystem, Med. Klin. **29**:15-19, 1933.

3. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Epilepsy: Paroxysmal Cerebral Dysrhythmia, Brain **60**:377-388, 1937.

rhythmicity. This activity, when properly amplified for gross recording, can be demonstrated to vary with age, physiologic state and mentation. It should be emphasized that the electroencephalogram reflects only the activity of the cortex; hence it is a record only of cortical conditions or of subcortical lesions as they are reflected through alteration in the overlying cortex.

There follows a brief résumé of the changing pattern from birth to adulthood: The electroencephalogram of the newborn infant consists of irregular, sinusoidal waves of high voltage (20 to 50 microvolts), occurring at the rate of ½ to 2 per second and arising chiefly from the parietal region. As the infant matures, occipital activity increases and dominates by 6 months of age. By the fourth year of life

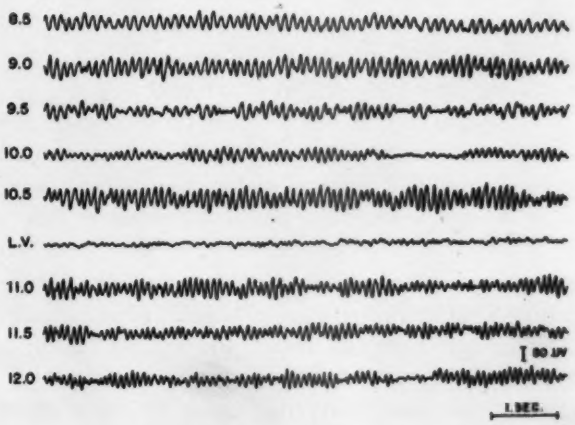

Fig. 1.—Electroencephalogram showing rhythms normally observed in adults. The time is indicated by the horizontal marker at the lower right, while amplitude is indicated by the vertical marker. Rates vary from 8½ to 12 cycles per second. Occasionally a low voltage (*L.V.*) record is obtained.

the rate is 9 to 10 per second, approximating that of the adult. A gradual decrease in voltage follows, so that by 19 years of age the pattern is typically adult. Figure 1 shows a series of recordings which demonstrates normal variations in frequency, amplitude and contour for the adult.

It was previously mentioned that mental activity and a variety of activities affect the electroencephalographic pattern. For example, the act of fixing attention tends to abolish the rhythm, increase the rate and "flatten" the curve. Sleep has the opposite effect, producing a slower rhythm with waves of higher amplitude. It is a common error to misinterpret brief "naps" as episodes of abnormal discharges. In general, children exhibit records slower than those of the adult, so that the waking electroencephalogram of the former resembles the sleep graph of the latter.

It was demonstrated by Lennox, Gibbs and Gibbs[4] that lowering the carbon dioxide or sugar level of the blood precipitates characteristic slowing of rhythms and may often initiate latent petit mal patterns.

Yet, even when these "physiologic" alterations are excluded, it is apparent that about 10 per cent of large groups of so-called normal persons show slight abnormalities. Less than 1 per cent of these persons exhibit pronounced abnormalities of the type observed in epileptic patients. These dysrhythmias may be considered as representing disturbances of subclinical proportions or some latent diathesis for a convulsive disorder. Conversely, 5 to 10 per cent of epileptic persons are reported to have normal records, although such results often indicate that: (1) the record taken may be too short; (2) a record made while the patient is asleep is essential to bring out the abnormalities, or (3) the disorder is subcortical in origin.

The conditions in which the electroencephalogram is most characteristically and consistently altered are those classified under epilepsy. In fact, each of the various forms of epilepsy usually displays a characteristic pattern. However, before individual descriptions of these patterns are presented, it should be stressed that they occur not only in the "idiopathic" convulsive disorders (and with increasing knowledge fewer types remain so labeled) but also in those disorders due to organic pathologic changes. This statement underscores the earlier one that electroencephalography is an adjunct to, but not a substitute for, careful clinical study.

In what respects, then, may the results of the electroencephalographic study be abnormal? First, the rate may be too fast, too slow or too irregular; next, the voltage (or amplitude) may be too high or too low, and, lastly, the form of the recorded waves may be abnormal, e. g., spikes, domes and cup-shaped or egg-shaped waves may appear. In general, a slow wave represents a period of sleep, coma or decreased activity, while a spike characterizes a movement, a convulsion or a period of tension.

Epilepsy may be classified into "idiopathic" and "symptomatic" types. Included in the former group are grand mal, petit mal and psychomotor seizures, while in the latter group are focal, jacksonian, myoclonic and akinetic attacks. It is characteristic of the "idiopathic" group that electroencephalographic changes are symmetric and are present simultaneously in all leads, whereas those of the "symptomatic" group are asymmetric and are often present in only one or several leads, but not in all.

4. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:277-297, 1938; J. Neurol. & Psychiat. **1**:211-225, 1938.

Figure 2 shows the characteristic patterns of the three types of idiopathic epilepsy. The electric activity of the cortex in grand mal is usually characterized by the appearance of fast waves prior to the seizure. The onset of a typical seizure is marked by the shower of waves occurring at a rate of 15 to 40 per second, each wave gradually increasing in voltage in crescendo pattern. This pattern corresponds to the tonic phase of the attack. As this phase attenuates, slower waves begin to appear which mix with the fast waves, gradually synchronizing with the clonic jerks that follow. The waves decrease to a rate of ½ to 1 per second and fall in voltage after the last clonic jerk. The postseizure stupor is marked by an almost flat record consisting of slow waves occurring at a rate of about 1 in three seconds. Before the stupor has ended, faster waves begin to infiltrate, gradually increasing in frequency, until the pattern normal for the patient (and his age) is reached. No typical interseizure patterns are observed in grand mal

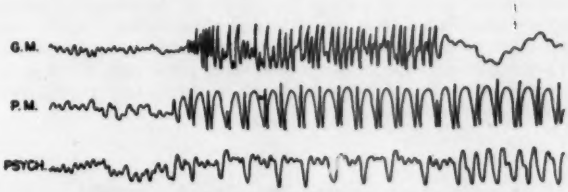

Fig. 2.—Electroencephalogram showing the paroxysmal patterns of the three types of idiopathic epilepsy. The first line shows the grand mal pattern (*G.M.*) which is characterized by high voltage spikes of 15 to 40 cycles per second. The second line (*P.M.*) indicates a petit mal pattern which is characterized by the spike and cusp waves at the rate of 3 per second. Psychomotor seizures (*PSYCH.*) are associated with high voltage, flat topped waves at the rate of 4 per second.

epilepsy, though often short runs of abnormal waves and rhythms occur.

In petit mal one finds a 3 per second pattern comprising a slow, dome-shaped wave and a fast, dart-shaped wave (or spike or cusp) (see fig. 2). This pattern usually appears simultaneously in all cortical areas. If confined to a single hemisphere or to a circumscribed region, it often indicates organic cerebral disease. Though the configuration usually recurs at the rate of 3 per second, the rate is faster at the beginning of a seizure and slower at its end. Moreover, in petit mal the characteristic pattern can be observed in interseizure records, being precipitated by active hyperventilation of the patient.

Psychomotor seizures are not common in children. They are characterized by flat topped waves occurring at a rate of about 4 per second, which are followed by 6 per second waves of high voltage (fig. 2).

The diagnostic value of electroencephalography is most evident in petit mal and psychomotor seizures, since characteristic patterns

are evident even between clinical episodes. Diagnosis is more difficult in grand mal because typical interseizure patterns are rare; it is common to observe many slow or fast runs of waves or occasional spikes between episodes, but usually nothing is seen that is characteristic. In consideration of this difficulty, it is recommended that diagnostic investigation during interseizure periods include a twenty minute record, using six to eight leads, with a period of hyperventilation lasting two to five minutes.

Fig. 3.—Electroencephalogram showing the types of paroxysmal patterns seen in symptomatic epilepsies. Fast spikes (*F.SP.*) and slow spikes (*S.SP.*) may occur synchronously with clinical myoclonic jerks. Short runs of slow or fast waves may occur in a pattern suggesting that of petit mal—the petit mal variant (*P.M.V.*). These groups of waves may occur irregularly or in runs, but generally they do not appear simultaneously in all leads.

Fig. 4.—Encephalogram showing petit mal variants arising from a focus in the left parietal region.

Examples of the type of paroxysmal patterns seen in symptomatic epilepsies are shown in figure 3. Irregularly appearing fast spikes (*F.SP.*) and slow spikes (*S.SP.*) are obvious in one or more leads. These spikes may be synchronous with clinical myoclonic jerks. In addition, short runs of slow or fast waves may appear. The pattern resembling in contour that of petit mal (hence tagged "petit mal variant"—*P.M.V.*) is actually associated with a clinical disorder distinctly different from petit mal. The pattern comprises a spike and a cusp or dome which is elongated and skewed and occurs at a rate of about 2 per second or less, generally displaying a constant focus. Moreover, it is usually associated with organic cerebral disease, e. g., hemi-

plegias or postencephalitic conditions. Clinically, the petit mal variant is often present in myoclonic or akinetic episodes and in the more drug-resistant disorders. The spikes seen in this pattern are often associated with manifest jerks. It is characteristic of the symptomatic

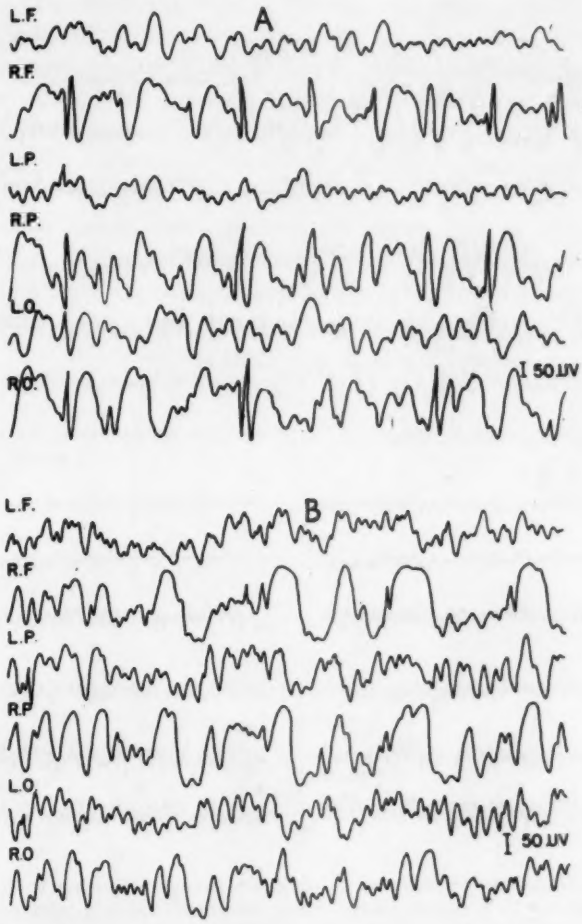

Fig. 5.—Typical six lead electroencephalograms from persons with symptomatic epilepsy. *A* is that of a 4 year old child with left hemiplegia, grand mal and petit mal following measles. Note that the greatest changes occur in the three leads from the right side of the brain. *B* shows the amplitude asymmetry and dysrhythmia of a left spastic hemiplegia, with convulsions beginning on the left side. Note the decided amplitude asymmetry, higher on the right, with dysrhythmia greatest in the right frontoparietal region.

epilepsies that abnormalities do not occur equally or simultaneously in all leads. It is often possible to localize the site of pathologic lesions by the asymmetric pattern (see fig. 4). Figure 5*A* and *B* illustrates typical six lead electroencephalograms in symptomatic epilepsy. *A*

is the record of a 4 year old child with left hemiplegia and grand and petit mal attacks which occurred after measles. It is obvious that the greatest changes are limited to the three leads from the right side of the brain. *B* illustrates the decided asymmetry in amplitude and dysrhythmia in a child with left spastic hemiplegia and convulsions.

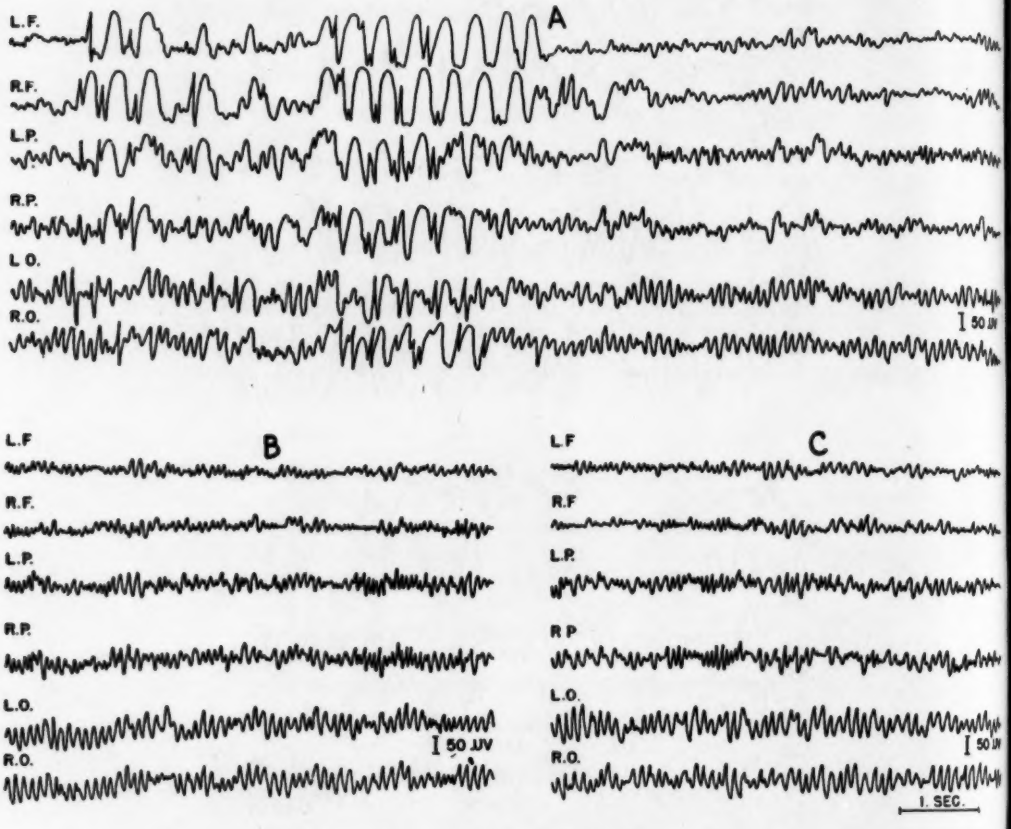

Fig. 6.—Electroencephalograms showing the changes resulting from the use of trimethadione. *A* is a record taken before trimethadione was administered. The patient had had only two grand mal attacks in her life, but 100 or more petit mal attacks per day. The chart shows frequent 3 per second wave and spike discharges of the petit mal type. The background activity is slightly fast. *B* is a chart for the same patient after she received trimethadione for eleven days, while *C* is a record taken after thirty-seven days. Patterns characteristic of neither grand mal nor petit mal are evident. The electroencephalogram shows no spontaneous seizure discharges, and none could be elicited with hyperventilation. The background activity is still moderately fast.

It is interesting to note that spikes more frequently are seen in the electroencephalogram of cerebral palsy with pyramidal tract involvement than in idiopathic grand mal epilepsy.

The electroencephalogram is of value not only in symptomatic interpretation and differential diagnosis but also in following therapy, a more recent development. Phenobarbital and sodium diphenylhydantoin ("dilatin"), though they may inhibit attacks of grand mal epilepsy, do not produce a similar corrective effect on the electroencephalogram. However, within the past two years, there has been introduced into the therapy of petit mal a drug that seems almost specific, namely trimethadione N. N. R. ("tridione"). Singular among the drugs utilized for epilepsy, it has a "normalizing" effect on the electroencephalogram, which mirrors the clinical improvement it effects (fig. 6). Thus, for the first time, the electroencephalogram can be utilized to follow therapeutic progress.

Recordings made during sleep are more apt to display latent abnormalities. However, since sleep normally slows the rhythm, and since the electroencephalographic waves of children are slower anyway, the "norms" for children are hard to establish. Thus, the interpretation of their records is fraught with difficulty and should be left to those experienced in this technic.

All the electroencephalograms used as illustrations were made by Dr. F. A. and Erna L. Gibbs.

TREATMENT OF IDIOPATHIC EPILEPSY

Introduction of a New Drug, "Thyphentoin"

M. G. PETERMAN, M.D.
MILWAUKEE

ANY CONSIDERATION of the treatment of idiopathic epilepsy must begin with a definition or a clear understanding of the disease and the phase of the disease to be treated. Whether "idiopathic" or "essential" or "cryptogenic" epilepsy is a symptom, a symptom-complex or a disease entity is of little consequence. Those workers who would argue this point invariably introduce some special designation for the syndrome which is usually understood to be a disease entity.[1] My definition follows: Idiopathic epilepsy is a chronic, usually progressive, inherited disorder of the brain, characterized by periodically recurring convulsions (major seizures), lapses (minor seizures, petit mal or petit mal variant attacks) or behavior disturbances (psychomotor episodes) which occur in a person with no other demonstrable, relevant neurologic disease and with no recognized pathologic lesion except the cerebral dysrhythmia elicited by means of the electroencephalograph. The attacks are usually precipitated by some sort of metabolic disturbance, probably associated with the acid-base mechanism.[2]

The potential cerebral disorder may be anticipated in children with a family history of convulsions who experience isolated convulsions associated with a high fever or with a gastrointestinal upset.[3] It often may be demonstrated by abnormal electroencephalograms before the disease becomes manifest.[4] It may usually be confirmed by typical electroencephalographic patterns between or during seizures

1. Panel Discussion: Section on Convulsive Disorders, American Chapter of the International League Against Epilepsy, Chicago, May 8, 1939. Buchanan, D.: M. Clin. North America **30**:163 (Jan.) 1946.

2. Peterman, M. G.: Ketogenic Diet in Treatment of Epilepsy, J A. M. A. **84**:1979 (June 27) 1925.

3. Peterman, M. G.: Convulsions in Childhood: Twenty Year Study of Two Thousand Five Hundred Cases, Am. J. Dis. Child. **72**:399 (Oct.) 1946.

4. Gibbs, F. A.; Gibbs, E. L., ad Lennox, W. G.: Electroencephalographic Classification of Epileptic Patients and Control Subjects, Arch. Neurol. & Psychiat. **50**:111 (Aug.) 1943.

after the disease has become established.[5] Each of the manifestations of this disease, i. e., grand mal, petit mal, akinetic seizures and psychomotor equivalents, registers a typical pattern on the electroencephalogram. These patterns are as distinctive as the well known clinical pictures.[6] The familiar hyperventilation test described by Rosett in 1924 has been widely used in attempts to precipitate seizures in persons with suspected or potential convulsive disorders.[7] Grant and Goldman produced convulsions by hyperventilation in 1920.[8] Foerster published a book, "Hyperventilation Epilepsy," in 1925.[9] Georgi and many others studied the effects of hyperventilation on epileptic patients.[10] Clinical seizures of the petit mal type often may be induced by deep breathing, which need not necessarily be carried to the point of alkalosis. Grand mal seizures are not often induced by this means. Hyperventilation is generally used in electroencephalography, and it usually produces a significant alteration in the brain wave pattern.[11] It is the only effective method known for the induction of the clinical symptoms or the typical electroencephalographic patterns. It has recently been suggested that trimethadione be used as a therapeutic test drug to induce major convulsions[3]. However, the severe major convulsions which follow the substitution of trimethadione for other drugs are probably the result of the withdrawal of anticonvulsant preparations. A similar result has been observed following replacement of other drugs with diphenylhydantoin sodium[12].

HISTORY

The history of epilepsy and its treatment has been thoroughly reviewed by Temkin in his recent book.[13] Lennox has briefly reviewed the introduction of the newer anticonvulsant drugs[14]. His suggestion

5. Baudouin, A.: Semaine d. hôp., Paris **22**:1209 (July 14) 1946. Baudouin, A.; Fischgold, H., and Rimond, A.: ibid. **22**:1217 (July 14) 1943.

6. Gibbs, F. A., and Gibbs, E. L.: Atlas of Electroencephalography, Cambridge, Mass., Lew A. Cummings Co., 1941.

7. Rosett, J.: Brain **47**:293 (Aug.) 1924.

8. Grant, S. B., and Goldman, A.: Am. J. Physiol. **52**:209 (June) 1920

9. Foerster, O.: Hyperventilation Epilepsy, Leipzig, F. C. W. Vogel, 1925.

10. Georgi, F.: Klin. Wchnschr. **4**:2053 (Oct. 22) 1925.

11. Gibbs, F. A.: Gibbs, E. L., and Lennox, W. G.: J. Pediat. **23**:497 (Nov.) 1943.

12. Fetterman, J. L.: Dilantin Sodium Therapy in Epilepsy, J. A. M. A. **114**:396 (Feb. 3) 1940.

13. Temkin, O.: The Falling Sickness: A History of Epilepsy from the Greeks to the Beginnings of Modern Neurology, Baltimore, Johns Hopkins Press, 1945, vol. 4.

14. Lennox, W. G.: M. Clin. North America **29**:1114 (Sept.) 1945; J. Pediat. **29**:356 (Sept.) 1946.

of priority in the use of caffeine for the treatment of petit mal must be corrected. Stargardter (1921) and Karger (1924) used caffeine in the treatment of petit mal and reported good results[15]. Penfield and Erickson stated that caffeine has been used extensively in the experimental study of epilepsy[16]. I tried this drug from 1923 to 1925 and observed that it had no permanent effect on the seizures. For many years I have also insisted that bromides, phenobarbital (or any of its trade brands) and diphenylhydantoin sodium have no effect on petit mal seizures[17]. It is well that Lennox has emphasized that diphenylhydantoin sodium may actually aggravate petit mal epilepsy.[14] Lennox' statement that "a ketogenic diet has been of distinct benefit to a minority of patients with petit mal, though if attacks are frequent freedom may be short lived,"[18] and DeJong's statement that "its efficacy (the ketogenic diet) is doubtful"[19] are hardly fair. The literature contains many reports by pediatricians that the ketogenic diet completely controls petit mal attacks, as well as grand mal seizures, in about one third of all patients adequately treated[20]. Another one third of the patients show considerable improvement. This result compares favorably with Lennox' report of his results with trimethadione (28[18] and 33 per cent[14] of patients free of petit mal), and the dietary treatment has resulted in no undesirable side effects or fatalities. Keith reports 53 per cent of epileptic children influenced favorably and 35 per cent "well" for four to twenty-two years[20e]. The

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15. Peterman, M. G., in discussion on Lennox,[18] p. 1074. Karger, P.: Deutsche med. Wchnschr. **50**:1531 (Nov. 7) 1924. Stargardter, J.: Jahrb. f. Kinderh. **95**:230, 1921.

16. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., Charles C Thomas, Publisher, 1941, p. 360.

17. Peterman, M. G.: J. Pediat. **17**:114 (July) 1940.

18. Lennox, G. W.: Petit Mal Epilepsies: Their Treatment with Tridione, J. A. M. A. **129**:1069 (Dec. 15) 1945.

19. DeJong, R. N.: Effect of Tridione in Control of Psychomotor Attacks, J. A. M. A. **130**:565 (March 2) 1946.

20. (*a*) Helmholz, H. F.: Treatment of Epilepsy in Childhood: Five Years' Experience with Ketogenic Diet, J. A. M. A. **88**:2028 (June 25) 1927. (*b*) McQuarrie, I., and Keith, H. M.: Epilepsy in Children, Am. J. Dis. Child. **34**:1013 (Dec.) 1927. (*c*) Helmholz, H. F., and Keith, H. M.: Eight Years' Experience with the Ketogenic Diet in the Treatment of Epilepsy, J. A. M. A. **95**:707 (Sept. 6) 1930; (*d*) Proc. Staff Meet., Mayo Clin. **7**:406 (July 13) 1932. (*e*) Keith, H. M.: ibid. **22**:14 (Jan. 8) 1947. (*f*) Fisher, L.: Arch. Pediat. **52**:131 (Feb.) 1935. (*g*) Talbot, F. B.; Metcalf, K., and Moriarty, M.: Epilepsy: Chemical Investigations of Rational Treatment by Production of Ketosis, Am. J. Dis. Child. **33**:218 (Feb.) 1927; (*h*) Tr. Am. Pediat. Soc. **38**:30, 1926; (*i*) Boston M. & S. J. **196**:89 (Jan. 20) 1926. (*j*) Talbot, F. B.: Treatment of Epilepsy, New York, The Macmillan Company, 1930. (*k*) Eley, R. C.: J. Pediat. **3**:359 (Aug.) 1933. (*l*) Helmholz, H. F., and Goldstein, M.: Proc. Staff Meet., Mayo Clin. **12**:433 (July 14) 1937; (*m*) Am. J. Psychiat. **94**:1205 (March) 1938.

diet controls and does not aggravate grand mal. The resistance of most neurologists to simple dietary treatment is difficult to understand. Reese indicated a broader viewpoint.[21] The current pediatric textbooks and systems still carry extensive chapters on the value of the ketogenic diet.[22]

DRUGS

With the introduction of new drugs, it is especially important to distinguish pure petit mal from minor grand mal seizures. Most physicians do not make this differential diagnosis. Many children with petit mal have potential grand mal epilepsy, or it eventually develops. Electroencephalographic studies may be required to make the distinction.

Trimethadione is a welcome addition to the treatment of pure petit mal epilepsy[18]. It is the first drug introduced that will control a certain percentage of these seizures. If the drug can be made safe, it will become a desirable adjunct in the treatment of a disease that has resisted all previous treatment with drugs. The undesirable side effects, and particularly the fatalities, that have been reported following its use dampened the enthusiasm which greeted its introduction[23].

I have treated 21 children with trimethadione. Only 5 of these patients had uncomplicated petit mal. One child had akinetic epilepsy, or "nodding spasms," which did not respond to trimethadione. Of the 5 children with petit mal, 3 were completely relieved of seizures, but in 1 an anemia developed which required discontinuance of the drug. One patient became too drowsy and irritable to allow continued use, and 1 did not respond. Four patients with grand mal and petit mal seizures were treated with trimethadione and phenobarbital. Two of these children showed improvement, but the 2 others were not benefited. In 7 children with grand mal severer and more frequent seizures developed while they received trimethadione than they had ever experienced. Four children with major convulsions, the result of cerebral birth injury, responded to trimethadione with more seizures. Administration of the drug was started with 0.325 Gm.

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21. Reese, H. H.: Wisconsin M. J. **45**:1049 (Nov.) 1946.

22. McQuarrie, I., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 4, chap. 12. Peterman, M. G, in Litchfield, H. R., and Dembo, L. H.: Infancy and Childhood, Philadelphia, F. A. Davis Company, 1942, vol. 3, chap. 60, p. 2303. Nelson, W. E.: Textbook of Pediatrics (Mitchell-Nelson), ed. 4, Philadelphia, W. B. Saunders Company, 1946, p. 1097.

23. Mackay, R. P., and Gottstein, W. K.: Aplastic Anemia and Agranulocytosis Following Tridione: Fatal Case, J. A. M. A. **132**:13 (Sept. 7) 1946. Aplastic Anemia and Tridione, Current Comment, ibid. **132**: 26 (Sept. 7) 1946. Trimethadione, report of the Council on Pharmacy and Chemistry, ibid. **133**:320 (Feb. 1) 1947.

two or three times a day, and the dose was then increased if necessary to 0.975 Gm. three times a day. I consider larger doses too dangerous. As soon as occurrence of petit mal seizures was not observed for two weeks, the dose was reduced to 0.325 Gm. three times a day. Patients whose attacks were under control for two weeks or longer had no difficulties when the dose of the drug was reduced, but attacks recurred when it was discontinued.

A NEW DRUG

Nine months ago (June 1946) a new drug was made available for clinical use by the Lilly Research Laboratories. This drug "thyphentoin" (sodium 5,5-phenylthienylhydantoin) was first prepared in 1941. The anticonvulsant properties were demonstrated in cats by the electroshock method. The acute toxicity was discovered to be 226.6 plus-minus 5.78 mg. per kilogram of body weight. This drug is approximately one-half as toxic as diphenylhydantoin sodium. No clinical manifestations of toxicity were noted, and no tissue damage was demonstrated on microscopic study. No damage to the liver was observed. Preliminary studies were made on patients in 1942; the results were most effective in those with petit mal attacks.[24]

Sixty-four children with convulsions have now been treated with this drug. Most of these children are private patients under close supervision. All have been repeatedly checked with electroencephalograms. Of these children, 24 had grand mal, 12 petit mal and 6 had both types. One patient had akinetic epilepsy (or nodding spasms), 2 had chronic encephalitis, 16 had residues from cerebral birth injuries, 1 had microcephalia, 1 had subdural hematoma (drained surgically) and 1 had cerebral dysgenesis.

The results of treatment with "thyphentoin" in adequate doses are as follows: Among 24 children with grand mal, 6 have been free of convulsions; the condition in 15 was improved, and in 3 it was not improved. In 12 children with petit mal 4 have been free of seizures; 5 showed improvement, and 3 showed no improvement. Two of the children who experienced no improvement with "thyphentoin" have been free from attacks while receiving trimethadione. In 1 child mentioned previously, anemia developed, and he was again treated with "thyphentoin." The seizures were reported under control for three months. In 5 children with combined epilepsy, 3 have been free of seizures and the condition of 2 improved. Fourteen children with residues from cerebral birth injuries and convulsions were improved, and 2 were not improved.

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24. Data supplied by Lilly Research Laboratories.

"Thyphentoin" was given in a dose of 0.13 Gm. two or three times a day. This dose was increased when necessary to 0.39 Gm. three or four times a day. When the latter dose did not control seizures, the drug was supplemented in petit mal with trimethadione or in grand mal or combined epilepsy with phenobarbital. (If the capsule cannot be given by mouth, it may be punctured and inserted into the rectum.) Except for the 2 children described previously who responded to trimethadione after "thyphentoin" failed to control petit mal seizures, the addition of trimethadione to "thyphentoin" did not influence the results. Phenobarbital is an effective supplement to "thyphentoin" for grand mal seizures. Smaller doses of phenobarbital are required when "thyphentoin" is used.

The side reactions to "thyphentoin" were as follows: In 3 patients hypertrophy of the gums developed; in 4 ataxia, disequilibrium and incoordination developed, and in 2 a drug rash appeared. All reactions except the hypertrophy of the gums subsided promptly on withdrawal of the drug. The blood counts were not altered in any case.

SUMMARY

The present treatment of idiopathic epilepsy may be summarized as follows: The impending or active convulsion is best treated with sodium phenobarbital given subcutaneously in a dose of 0.016 Gm. to 0.130 Gm. every four hours until the patient has been free of convulsion for twenty-four hours. If the convulsion persists, chloroform or vinyl ether U. S. P. ("vinethene") should be given by inhalation, or tribromoethanol ("avertin") may be given in a dose of 75 mg. per kilogram by rectum. As soon as the convulsion is under control and the patient has regained consciousness, an anticonvulsant preparation should be given by mouth every six hours.

Opium derivatives and ether are distinctly contraindicated. This statement must be emphasized.

Uncomplicated grand mal epilepsy is best treated with phenobarbital U. S. P. in a dose dependent on the duration and frequency of seizures. From 0.016 to 0.1 Gm. should be given every six hours regularly. Further recurrence of convulsions demands an increase in the dose to the point of tolerance. Once the seizures are under control, the drug must be continued in the effective dose for at least one year, or until a normal electroencephalogram is obtained. The drug must never be discontinued abruptly, but the dose should be tapered off gradually for a period of two years. No known drug is the equal of phenobarbital in the treatment of grand mal epilepsy. Phenobarbital is almost a specific and may be used for a therapeutic trial. The side reactions are few and unimportant. None of the known anti-

convulsant preparations can be used to replace phenobarbital abruptly.

Uncomplicated petit mal epilepsy may be treated with "thyphentoin" in the dose described in the present paper. The patient should be kept under observation for toxic reactions, such as hypertrophy of the gums, rash, vertigo and disequilibrium. If the seizures are not controlled or if toxic symptoms appear, trimethadione should be given a trial in the dose indicated. The patient must then be kept under close observation for toxic reactions. The blood count must be checked every two weeks for evidence of depression of the bone marrow.

Children with combined grand and petit mal and/or psychomotor epilepsy may be given a trial treatment with "thyphentoin." Failure of response to this drug, and particularly the recurrence of grand mal seizures, requires the addition of phenobarbital.

The safest and most logical treatment of all idiopathic epilepsies, especially the combined types which are the commonest in children, is the ketogenic diet. This treatment is the only one aimed at the correction of the basic metabolic disorder. A new milk derivative, plastic dehydrated cream, will greatly simplify the problem of obtaining fat.

411 East Mason Street (2).

COMPLICATIONS OF ACUTE PYOGENIC MENINGITIDES

ARCHIBALD L. HOYNE, M.D.
CHICAGO

IT IS NECESSARY to compare the past with the present in order to appreciate fully the altered course of the meningitides. Until nine years ago, recovery from any form of bacterial meningitis, other than the meningococcic variety, was a rare event. Therefore, prior to 1937 opportunities to study many of the complications of meningitis were limited to those patients in whom Meningococcus was the inciting factor. Consequently, this discussion will relate chiefly to meningococcic meningitis.

Complications may occur at any stage of the infection. Petechiae are sometimes classified as complications and appear early, often preceding any clinical evidence of meningitis, which, as a matter of fact, may not develop.[1] As a rule, no forms of meningitis except those with meningococcic infections include petechiae. Some years ago, Gordon[2] reported that 59.54 per cent of his patients with epidemic meningitis had petechiae. During the last four years in Chicago, petechiae were present in approximately 63 per cent of patients with this disease.

Whether petechiae are to be classified as a complication of meningitis or not, it would seem that massive hemorrhages into the adrenal glands of patients with meningitis should be so classified. However, with the Waterhouse-Friderichsen syndrome, which is almost invariably attributed to a meningococcic infection, meningitis may not be evident. In reality, if meningitis is present, it does not constitute the primary condition but is itself a complication of an infection of the blood stream. In some forms, meningitis may be the result of a direct extension of an infective process from a known focus, as the ears, nose or sinuses.

Subconjunctival hemorrhages are occasionally observed and are not likely to be serious; but hemorrhages from the mucosa of the stomach and intestine usually signify disastrous consequences. Practically all the hemorrhagic conditions which develop with meningococcic infections occur soon after the onset of symptoms. Hemor-

1. Hoyne, A. L.: Meningococcia (Meningococcic Meningitis): A New Remedy, Arch. Pediat. **52**:418-421 (June) 1935.

2. Gordon, J. E.: Medical Report of the Herman Kiefer Hospital, for the Five Year Period 1927-1931, Detroit Department of Health, Division of Epidemiology, 1932, sect. 22.

rhage, other than in the form of petechiae, is a rare event in any type of meningitis. Nevertheless, I have seen hemorrhage into the lungs in meningococcic infections and into the pleural cavity in influenzal meningitis. Herpes simplex has been more or less commonly associated with various types of meningitis for many years, but to me it never seemed to deserve much attention. However, it occurred in 15 per cent of our patients in one series prior to the introduction of chemotherapy. With the use of sulfonamide drugs, herpes about the nose and mouth frequently appear two or three days after treatment is begun. Other portions of the body are seldom affected.

Arthritis is usually regarded as the commonest complication of meningococcic meningitis. Sophian[3] stated that it occurred in 10 to 15 per cent of his patients, whereas Gordon's percentage was only 3.3 among 1,090 patients. The figure at Municipal Contagious Disease Hospital (Department of Health, Chicago) during the past four years was 9.6 per cent. Wrists, ankles, fingers and toes are most likely to be affected, and the involvement is sometimes noted before a diagnosis of meningitis has been made. When the knee is concerned, the condition is not apt to occur so early. Ordinarily, there is no suppuration in the joints, and the inflammation subsides within a few days. However, I recall 2 cases in which drainage of pus was necessary, in 1 from the knee and in the other from the shoulder joint.

Although convulsions may usher in an attack of any form of meningitis, recurrences after the onset are unusual except in the tuberculous form and, less often, in the influenzal type.

The two most serious complications are those which involve the eyes and the ears. These organs of special sense may be affected either early or late. As a rule, Meningococcus is the responsible organism. At the onset of illness, reaction to light is noted but accommodation is sometimes sluggish. Except in tuberculous meningitis the pupils are rarely unequal, and in that condition inequality may not be observed until late. Conjunctivitis in meningococcic meningitis should always be viewed with alarm, as it may be the first sign of impending endophthalmitis and probable loss of vision. The condition is often unilateral, but both eyes may be affected. Among 233 patients[4] treated at Municipal Contagious Disease Hospital in 1933 to 1935, 17 (7.2 per cent) lost the sight of one or both eyes. All these patients received serum intraspinally. Lazar[5] reported endophthalmitis in 5.2

3. Sophian, A.: Epidemic Cerebro-Spinal Meningitis, St. Louis, C. V. Mosby Company, 1913, p. 134.

4. Hoyne, A. L.: Meningococcic Meningitis: Importance of Intravenous Therapy, Illinois M. J. **68**:307-311 (Oct.) 1935.

5. Lazar, N. K.: Early Ocular Complications of Epidemic Meningitis, Arch. Ophth. **16**:847-856 (Nov.) 1936.

per cent of 575 patients with meningococcic meningitis. After intraspinal therapy was abandoned at Cook County Contagious Hospital and all serum was administered intravenously,[6] ocular complications seldom developed after hospitalization. During the past four years at Municipal Contagious Disease Hospital my colleagues and I have treated more than 700 patients with meningococcic meningitis, and in that group the only ocular complications which involved loss of vision were present when the patients were admitted.

Deafness may be a greater impairment than loss of sight in one eye. It may result from meningococcic infections without meningitis.[7] When deafness occurs, it is nearly always bilateral. Although this complication is associated almost entirely with meningococcic meningitis, I have seen it develop in patients with pneumococcic meningitis on a few occasions but before streptomycin was available, never in those with influenzal meningitis.

Rarely is the first complaint made at the onset of meningococcic meningitis that of inability to hear. If loss of hearing is complete, the likelihood that it will ever be restored is small. Should this catastrophe befall an infant, the child will grow up a deaf-mute—he cannot hear and he has never learned to talk.

Among the group of 233 patients previously alluded to, 20 (8.5 per cent) were completely deaf at the time of discharge from the hospital. Brinton[8] stated that in World War I deafness occurred in 5 per cent of patients. As with ocular complications, loss of hearing became much less frequent after discontinuance of intrathecal therapy. Among 669 patients in recent years, we have had only 16 (2.4 per cent) who lost hearing ability. In 10 patients deafness was complete; in the other 6 it was only partial. If deafness is only partial, the hearing may be decidedly improved. Other aural complications, including suppurative otitis media, are extremely rare, but otitis media may be the primary focus for meningitis caused by Streptococcus, Pneumococcus, Staphylococcus or Klebsiella pneumoniae (Friedländer's bacillus).

Among the various forms of paralysis, the one affecting the bladder is commonest, yet this complication occurs in only about 1 per cent of patients. Oculomotor disturbances come next in frequency, with strabismus leading this field but occurring in less than 1 per cent of patients. Diplopia, ptosis and facial paralysis are infrequent. Rarely

6. Hoyne, A. L.: Treatment of Meningococcic Meningitis Without Intraspinal Therapy, Nebraska M. J. **21**:321-325 (Sept.) 1936.

7. Leichinger, H., and Abelson, S. M.: Deafness Associated with Meningococcemia, Arch. Otolaryng. **26**:306-309 (Sept.) 1937.

8. Brinton, D.: Cerebrospinal Fever, Baltimore, Williams & Wilkins Company, 1941.

have we had instances of paralysis of an arm or leg or complete hemiplegia, and normal function was restored with recovery in each patient.

Endocarditis is seldom diagnosed as a consequence of meningitis during the life of the patient, and pericarditis less often. If the latter disease occurs with effusion, the condition is generally suppurative and almost certainly fatal. Sometimes it is inferred that myocarditis is not an unusual complication, but experience does not uphold such a contention.

Hydrocephalus, either internal or external, is a possible complication and is more frequent than nephritis, which is rare. Gangrene of skin, toes or fingers, cerebral abscess or thrombosis and residual mental deficiency are seldom observed. Occasionally, defects in the special senses and personality changes develop after convalescence from meningitis.

The assertion is sometimes made that all patients with meningitis have encephalitis. It is true that such an assumption might be based on observations at autopsy. However, clinical evidence to support such a statement in regard to patients who survive is lacking. Encephalitis is an extremely unusual complication in the opinion of most experienced observers.

The recurrent and chronic forms of meningitis may be classed as complications. Formerly, both these conditions were of fairly common occurrence. In Gordon's series the patients with these complications exceeded the number of patients who had arthritis.

Lobar pneumonia is infrequent, but bronchopneumonia is responsible for most of the deaths.

All the complications thus far enumerated have been associated with the various forms of meningitis before the advent of chemotherapy. Even today with improved methods of treatment, the same complications may occur, but, with the exception of arthritis, their incidence is decidedly lower.

There is another group of complications, which, in retrospect, some of us will concede need not have occurred during the era of serum therapy. I refer to the evils linked with intrathecal treatment and the numerous spinal taps for "relieving intracranial pressure." Illustrative of the customary experience of that time, I refer once again to Gordon's excellent statistics for meningococcic meningitis. In his series of 1,090 patients, 8,713 spinal punctures were made, 1,206 cisternal and 10 intraventricular. The average number of spinal taps alone was 9.6 for recovered patients. However, with no intrathecal therapy, we had far in excess of 1,000 recovered patients who averaged less than one spinal tap.

The decline in complications and the extremely low fatality rates of recent years are generally attributed solely to the use of the sulfonamide compounds and the antibiotic substances. However, it should be borne in mind that present day treatment seldom includes the intrathecal administration of serum, and frequently no intrathecal treatment is given at all. After abandoning intrathecal therapy at Cook County Hospital in 1934, and somewhat later at Municipal Contagious Disease Hospital, we often had as few complications and as low fatality rates with the exclusive use of antiserum intravenously as we have had since with sulfonamide therapy. Frequent drainage of spinal fluid is another unnecessary procedure that may be a contributing factor in causing complications. As a rule, not more than one spinal tap is required for any form of meningitis, and, when it is made, it should be necessary only for the purpose of establishing an accurate diagnosis. In three and three-quarter years, 1943 to 1946, among nearly 700 patients with meningococcic infections at Municipal Contagious Disease Hospital, no blocks in the circulation of cerebrospinal fluid were demonstrated. The patients averaged less than one spinal puncture. More than 200 patients (37.9 per cent) had no punctures, the diagnosis being confirmed by smear from petechiae or by culture of the blood. In Gordon's series of patients given intrathecal treatment, 101 (10 per cent) had spinal blocks and 25 (2.29 per cent) had cisternal blocks.

Complications Among 1,000 Patients with Meningococcic Meningitis with and Without Intrathecal Therapy

	Intrathecal Serum	Exclusive Intravenous Serum	Chemotherapy No Intrathecal Treatment
Lumbar punctures	Average 10	Less than 1	Less than 1
Spinal blocks	Frequent	None	None
Injury to the intervertebral disk	Rare	None	None
Opisthotonos	Common	None	None
Secondary meningitis	Rare	None	None
Hydrocephalus (infants)	Frequent	Uncommon	Uncommon
Recurrent meningitis	Occasional	None	Rare
Serum sickness	70%	70%	None
Deafness	8.5%	Less than 3%	3%
Endophthalmitis (loss of vision)	5%	Less than 1%	Less than 1%
Chronic meningitis	Occasional	None	None
Decubitus ulcers	0.5%	None	None
Hematuria	None	None	17 to 50%
Time for recovery	21 to 28 days	6 to 10 days	6 to 10 days

Superficial infections and, sometimes, secondary forms of meningitis as the result of numerous punctures are no longer likely to be witnessed. Likewise, with a single lumbar puncture, the possibility of injury to intervertebral disks is decidedly lessened. Without intrathecal treatment, opisthotonos is no longer the rule but the exception. We observe that the only patients who present this condition now are those whose treatment has been long neglected or those who receive intrathecal therapy.

There are perhaps many physicians who reluctantly abandoned intrathecal therapy when the sulfonamide compounds finally displaced antiserums and who have reverted to intraspinal treatment. Originally type B anti-influenza serum was recommended for intrathecal as well as for intravenous administration. Penicillin is given intrathecally by some clinicians, and administration of streptomycin by the same route is advised. We have never given anti-influenza serum intrathecally, but we have administered penicillin and streptomycin in that manner. It is true that penicillin is effective in eradicating temporarily certain organisms, namely, pneumococci, streptococci and staphylococci, from the spinal fluid. But when intrathecal injection of penicillin is discontinued, our experience has been that relapses are not unusual. Moreover, blocks may possibly develop as well as all the other disadvantages which accompany frequent lumbar punctures.

Other possible complications are hematuria, blocked ureters and cutaneous eruptions, which may occur in the course of treatment with the sulfonamide drugs. These conditions are related entirely to the therapeutic agent, but they may peril or retard the recovery of the patient with meningitis.

COMMENT

Withholding intrathecal therapy in all forms of meningitis is an important means of diminishing complications and lowering fatality rates.

3026 South California Avenue.

ALLERGIC MANIFESTATIONS IN THE CENTRAL NERVOUS SYSTEM

BRET RATNER, M.D.
NEW YORK

IT WOULD TAKE one into too controversial a field to attempt to cover all the allergic manifestations of the central nervous system which might be attributed to the hypersensitive state. I shall, therefore, omit from consideration migraine, histamine cephalalgia, Ménière's syndrome, epilepsy and certain convulsions of infancy, which have all been charged to allergy by one or another investigator.

My remarks will be confined to an analysis of the cerebrospinal effects occurring in serum sickness and from serum allergy[1]. The allergic manifestations resulting from the parenteral injection of foreign serum lend themselves to accurate appraisal. The time of entrance of the otherwise innocuous substance can always be ascertained; the material is not complicated, nor does it possess primary toxicity when properly prepared.

Consideration of allergic encephalopathies from smallpox or rabies vaccines, drugs and antibiotic substances is somewhat complicated because of the primary toxicity of drug and antibiotic substances on the one hand and the complexity of the viruses on the other. One cannot be certain whether the reaction is due to allergy or is the result of these factors.

Since neurologic allergic sequelae can occur from the entrance of an innocuous foreign serum into the body, similar sequelae from the use of such substances as sulfonamide drugs, penicillin, streptomycin and virus vaccines may be appraised.

No mention of neurologic complications following the administration of serum was made by von Pirquet and Schick[2] or their predecessors. This freedom from complication may be accounted for by the fact that it was not until the period between 1908 and 1915 that the intrathecal route was adopted for the administration of therapeutic

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From the Department of Pediatrics, New York University College of Medicine.

1. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, Williams & Wilkins Company, 1943.

2. von Pirquet, C., and Schick, B.: Die Serumkrankheiten, Leipzig, F. Deuticke, 1905.

serums. Furthermore, neurologic complications usually occur in patients more than 21 years of age, and the majority of cases studied by the earlier investigators were in children to whom diphtheria antitoxin and antiscarlatinal serum were administered[1].

Since 1908, it has slowly become evident that the brain and meninges, the spinal roots and the peripheral nerves may be the sites of more or less servere allergic reactions. These sequelae, as a rule, subside, leaving few, if any, residuas. Notwithstanding the many reports of such allergic episodes, they are relatively rare. If the frequent occurrence, however, of headache, nausea, vomiting and neuralgia in the usual and well known type of serum disease constitutes a syndrome of neurologic origin, then a mild form of serum disease of the nervous system is frequent. It is further possible that many of these neurologic complications have been entirely overlooked in other situations.

MENINGEAL SYNDROMES

I have differentiated three types of meningitis following serum injections: (1) serum sickness meningitis, (2) aseptic or serum meningitis and (3) allergic meningitis.

Serum sickness meningitis results from an extrathecal injection of serum and manifests itself during the course of ordinary generalized serum sickness and accelerated serum allergy. The spinal fluid shows a preponderance of lymphocytes.

Aseptic or serum meningitis results from the primary contact of the meninges with the serum after intrathecal injection. It is nonallergic, and polymorphonuclear cells are predominant in the spinal fluid.

Allergic meningitis may be a sequence to intrathecal injection of serum in a person who has been sensitized by previous experience with the serum. It also is characterized by the presence of predominantly polymorphonuclear cells in the spinal fluid, but coupled with this sign are the profound allergic reactions of the nervous system.

I am of the opinion that the cytologic study of the spinal fluid may aid in differentiating meningeal reactions[1]. Thus, any reaction that is predominantly lymphocytic would connote an extrathecal pathologic condition, such as obtains in those diseases producing serous meningitis, e. g., the lymphocytic phase of tuberculous meningitis, polioencephalitis, the lymphocytosis observed in parasyphilitic diseases of the central nervous system and choriomeningitis. On the other hand, when there is an increase predominantly in polymorphonuclear cells in the spinal fluid, I believe it is evidence that some foreign substance, chemical, bacterial, virucidal or serous, has gained direct entrance into the spinal canal.

During the period of general serum sickness, headache, nausea, vomiting and neuralgia frequently occur. The observation of a moderate increase in lymphocytes and of increased fluid pressure in the cerebrospinal fluid during the early stage of serum sickness indicates that a definite neurologic disorder is responsible for the headache, nausea and vomiting.[3] Delahet[4] reported a group of cases in which convulsions and coma were exhibited, symptoms he grouped under the term *chocbulbaire.* In 1 of his cases the reaction followed the intravenous injection of a small amount of serum. The author attributed the reaction to the irritation of the meninges. Such a condition, then, is an accelerated allergic reaction in the meninges of a person previously sensitized; it is not strictly serum sickness, but the mechanism is very similar.

Serum sickness of the meninges resembles serous meningitis which occurs in infancy and occasionally in childhood, but it differs with respect to the etiologic agent. Serous meningitis develops as a symptom secondary to various acute infections, such as typhoid, measles, influenza, whooping cough, gastroenteritis and, particularly, pneumonia, inflammation of the middle ear, trauma involving the head (without suppuration) and syphilis.

The existence of serous meningitis as an entity is now admitted. The designation applies properly to acute cases with meningeal symptoms, in which the cerebrospinal fluid is increased in amount, under slight increase in pressure with a small increase in protein content and the presence of about 10 lymphocytes per millimeter. Bacteria are never seen in such spinal fluids. Microscopic examination of the meninges shows a certain amount of cellular infiltration.

Corroboration of the concept that serum injected extrathecally will, if it affects the meninges, result in a lymphocytic response is found in the first reported case of optic neuritis by Mason[5]. His patient received 500 cc. of antipneumococcic serum, and eleven days later severe general urticaria developed, with a rise in temperature to 104 F. Serum sickness persisted for two weeks, and three days later the patient became drowsy and dull. In addition to the findings on ophthalmoscopic examination, the cerebrospinal fluid showed an increased pressure; globulin was present, and there were 150 lymphocytes per cubic millimeter.

3. de Lavergne, V., and Abel, E.: Des modifications du liquide céphalorachidien au cours des réactions sériques, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:488, 1926.

4. Delahet, M.: Sur un case du méningíte sérique post-méningocoque: Traitement par vaccination antisérique, Bull. et mém. Soc. méd. d. hôp. de Paris **44**: 1272, 1920.

5. Mason, V. R.: Optic Neuritis in Serum Sickness, J. A. M. A. **78**:88 (Jan. 14) 1922.

The introduction of a foreign protein into the theca may produce a primary nonallergic effect, and at times the effect may be so serious as to cause death in a few hours from medullary and cerebral edema. However, this primary reaction of the meninges must not be confused with allergic meningitis. The latter condition is a true hypersensitive reaction of the meninges which occurs only after a latent period following the primary sensitizing injection.

The situation that may arise from repeated intrathecal and intravenous injections is beautifully exemplified in a case reported by Sheppe,[6] which can be described either as a case of allergic meningitis or as one of local cerebromeningeal anaphylactic shock. Meningococcic meningitis developed on the sixth day in a laboratory technician who was infected by the spinal fluid of a patient which spurted into her face. Intraspinal treatment was instituted with twelve daily injections of specific serum. Six days later, the symptoms recurred, and again 15 cc. of serum was given. One hour later, the patient lapsed into unconsciousness. Opisthotonos was pronounced, and convulsions ensued. Lancinating headache and complete loss of sphincter control were present.

Several days later, after complete subsidence of meningitis, 0.1 cc. of serum was given intravenously in an attempt at desensitization. Within an hour the previously described symptoms of coma, convulsions and opisthotonos recurred. Three hours later these severe symptoms subsided. This case shows in a striking manner the danger of giving injections at a time when sensitization is likely to be established, and I believe it clearly defines the type of allergic meningitis under discussion.

Essentially, an immediate anaphylactic reaction occurred as the result of an intraspinal injection of serum given six days after a preliminary series of twelve daily injections. Local sensitization of the brain and meninges was apparently established some time during the eighteen days after the primary injection. Even more remarkable is the occurrence of local cerebrospinal anaphylaxis from the serum given intravenously several days later.

CEREBRAL SYNDROMES

The cerebral syndromes of allergy may be characterized by choked disks, meningeal irritation, the Kernig and Babinski signs and by such additional manifestations as aphasia, alexia, hemianopsia and hemiplegia. The spinal fluid pressure is much increased. The cellular reaction is slight. Associated paralysis of the cranial nerves or a bulbar

6. Sheppe, W. M.: The Reaction of the Meninges to Therapeutic Serum, Am. J. Clin. Path. 1:77, 1931.

syndrome with or without tetraplegia may occur. These syndromes are of cerebroneural origins.

Among the other related cerebral complications which have been described[1] are optic neuritis, retinal edema and iritis.

Ocular involvement in serum sickness apparently has been the subject of few reports, but they are extremely convincing and should awaken interest.

Other reports of recurrent paralysis of the larynx and of involvement of the auditory nerve are of equal importance in showing that the cerebral form of allergy may or may not be combined with involvement of the cranial nerves.

The physiologic and pathologic changes resulting from the cerebrospinal allergic manifestations are the result of a combination of spastic, vascular disturbances, with consequent edema causing pressure symptoms. This evanescent pathologic condition accounts for the generally good prognosis in all of the neurologic sequelae.

If the several phases of the hypersensitive reactions are borne in mind, they should aid in the diagnosis and differentiation of allergic cerebrospinal reactions which may follow the use not only of serum (allergy to which may be used as a yard stick) but also of such diverse substances as the sulfonamide compounds, penicillin, streptomycin, "hapamine" (a chemical combination of histamine and despeciated horse serum globulin), virus vaccines, food and other allergens.

50 East Seventy-Eighth Street.

CONVULSIONS AND ACUTE INFECTIONS

JOHN A. TOOMEY, M.D.
CLEVELAND

THE COMMONEST cause of convulsions in children is a high fever associated with an infectious disease. If there are a half million epileptic persons with convulsions each year, then comparatively, millions of patients with infectious fevers have convulsions. Observation for a quarter of a century has taught me to be optimistic about their outcome.

Convulsions may occur at any time during the course of an infectious disease, but usually they take place at the onset when the temperature is highest and when a rash, if present, is most prominent. They occur at any age but are commonest from birth to 2 years of age.

Convulsions may be localized and unilateral or generalized with no localization, or a combination of reactions may be present. Objectively, convulsions are similar, no matter what the cause. In the majority of patients but one attack occurs, the reaction being so severe that medical aid is immediately sought and procedures adopted to prevent other attacks. With the use of antibiotic substances and sulfonamide drugs, the incidence of this condition has sharply decreased.

Why convulsions occur, no one knows. To say that they are caused by toxins, that the cortex is less stable, that the chemical balance has changed, that there is an aberrant discharge of nerve impulses to the muscles, causing muscular contractions, is begging the question. I have never tried consciously to produce convulsions clinically, but I have done it accidentally, when 2 patients with encephalitis were given too much fluid intravenously. The convulsions which occur with fever do not ordinarily cause death. If the patient dies, it usually is from the disease or from one of its complications.

It has been stated that from 15 to 20 per cent of those persons who have convulsive attacks with fever have recurrences later. Such an incidence is not my experience. Attacks recurred in 2 to 3 per cent, and damage to the brain with mental involvement was observed in less than a fraction of 1 per cent of my patients.

Certain infections are more apt to be accompanied with convulsive seizures than others. If the condition called terminal convulsion which appears just before death from any disease—the convulsive, tetaniform, stretching muscular movements which accompany the act

of dying—is ignored, the commonest conditions causing convulsions are infections of the upper and lower parts of the respiratory tract due to any bacterium (Pneumococcus, Hemophilus influenzae and others) and, especially, infections of the middle ear of infants.

With whooping cough, the convulsions may be general. Usually, not more than four or five episodes occur, and rarely do the attacks become repetitive to the point that the patient goes into an epileptiform fit. I have seen 29 such persons among the thousands admitted to the hospital in the past twenty-five years. Convulsions in this disease are followed occasionally by hemiplegia, from which, with persistent physical therapy, recovery is possible within a few months. Occasionally, however, the patient does not completely recover and is left with a residuum of clawlike fingers and homolateral paralysis of the facial nerve, or becomes, as did 1 patient, a spinal animal.

Uremia associated with scarlet fever is ushered in by an elevated temperature; often convulsions occur within a few weeks after the initial symptoms appear. These convulsions may persist for a short time, but they respond well to ordinary therapy, and never in my experience has any residuum resulted.

Patients with measles may go into a somnolent state following the convulsions, which may last as long as a month. After an acute infection, such as chickenpox, measles, influenza and the like, such a condition may supervene; that is, the patient may become lethargic after the convulsion. The patient usually comes out of the coma within at least two weeks. He may recover even after a continued period of four weeks of lethargy with no mental retardation. However, if such a state persists longer than twenty-one days, there is cause for worry, as permanent mental damage may result, especially when the patient has a normal temperature and a continued large amount of protein in the spinal fluid.

The ordinary type of encephalitis is not commonly associated with convulsions. Occasionally, convulsions occur with pyelitis, poliomyelitis or mumps. I have never seen permanent mental changes in a patient with parotitis, although convulsions in this disease are not at all uncommon.

The patient with rabies has convulsions, but these are part and parcel of the disease. The same observation may be made of tetanus, but in this disease the convulsions can be controlled, and if they are controlled the patient usually recovers. It is much more important to control the convulsions than to give specific antitoxin.

Any acute infection may be accompanied with convulsions. The most important thing is not that the person has convulsions but the discovery of their cause and their subsequent control. If somnolence supervenes, it should be terminated. I cannot subscribe to the theory

that convulsions tend to create a trigger-like sensitivity of the cortex, so that it is ready to respond more easily in the future to some other infection. Doubtless, such instances occur in patients who come to a specialized clinic, and their numbers impress the physicians in the clinics. However, when the large number of persons with infectious diseases is considered, the incidence of convulsions becomes small indeed.

3395 Scranton Road.

DISCUSSION

QUESTION: Is the surgical treatment of hydrocephalus of any value?

DR. T. J. PUTNAM, Beverly Hills, Calif.: It is of definite value. Surgical treatment is effective in about 40 per cent of well chosen cases. The cases have to be selected, for obviously an operation on an infant with damaged mentality is useless. However, for babies with well preserved mentality who show a great increase in intracranial pressure, this operation is a simple and satisfactory one.

QUESTION: Dr. Putnam, will you describe the exact technic of percussion in eliciting Macewen's sign and discuss its proper evaluation?

DR. T. J. PUTNAM, Beverly Hills, Calif.: All I know how to do is to tap with my finger. As a matter of fact, it is often more of a sensation than a sound. One feels that the fluid vibrates under the percussing finger, a sound which might be compared to that obtained from a ripe watermelon.

QUESTION: Is arteriography a dangerous procedure?

DR. T. J. PUTNAM, Beverly Hills, Calif.: Not according to the literature. The accidents are few. I think a good many of them have gone unrecorded. I personally feel that neither is it an innocuous procedure nor is it one that I should care to undertake unless some definite end was to be achieved which could not be gained by more conservative means. The procedure is of great value, however, in cases of suspected aneurysm or angioma.

QUESTION: Since the prognosis of most gliomas is so poor, should patients with cerebellar tumors be operated on?

DR. T. J. PUTNAM, Beverly Hills, Calif.: The suggestion has been made that some patients with cerebellar tumors might be treated with radiation without surgical intervention. Personally, I am loath to accept this suggestion as a rule. It seems to me that it is not always possible to make a definite differentiation between the astrocytomatous cyst, which can be so readily treated surgically, and the malignant tumors of the third ventricle, which respond better to radiation. The astrocytomas do not respond well to radiation. I believe it is wisest to expose the cerebral fossa and to make a biopsy of the tumor. If it is an astrocytoma, an attempt should be made to remove it; if it is a medulloblastoma or ependymoma, it should be treated with radiation.

QUESTION: Is electroencephalography of any help in the diagnosis of cerebellar tumors?

DR. T. J. PUTNAM, Beverly Hills, Calif.: I find it of small help. In one quarter to one half of the cases some evidence of damage over the occipital lobes is recorded, but this is not a reliable sign of localization. The absence of focal disturbance elsewhere is of some negative value.

QUESTION: Is lumbar puncture ever safe or advisable in cases of suspected brain tumor in children?

DR. T. J. PUTNAM, Beverly Hills, Calif.: This point I think I covered fairly well in the lecture. I think the dangers have been overrated, especially when there is no evidence of extremely high intracranial pressure. It is usually an innocuous procedure which often saves one from doing pneumoencephalographic studies and often obviates the need of further diagnostic procedures, some of which have a certain greater danger than lumbar puncture. It should be done with the patient under sedation with barbiturates.

QUESTION: Since irradiation is the treatment of choice for the medulloblastomas, would it not be worth while to try radiation treatment before operation on patients suspected of having this type of tumor?

DR. T. J. PUTNAM, Beverly Hills, Calif.: That question is substantially the same as the previous one. If there were a more certain method of diagnosis, I should think the suggested procedure would be a perfectly reasonable one, but it would be sad to overlook the chance of saving the eyesight of the patient with astrocytoma while trying radiation. Even in the presence of a medulloblastoma, I believe radiation is safer after decompression has been done. Sometimes radiation causes edema and, unless space has been provided artificially, there is definite danger of pressure on the brain stem.

QUESTION: Dr. Perlstein, are you now prescribing the elixir of trimethadione which has just been made available commercially? If so, how stable is this preparation?

DR. M. A. PERLSTEIN, Chicago: The preparation is now on the market. It is not only stable but, more important, it is palatable. A sugar tablet form is available also.

QUESTION: Are the changes seen in the electroencephalogram transmitted by heredity?

DR. M. A. PERLSTEIN, Chicago: To a great degree the general dysrhythmia is transmissable, though the exact paroxysmal pattern may not be. If electroencephalograms of the parents of children who have epilepsy are made, a dysrhythmia will be apparent in at least one of the parents in a majority of instances.

QUESTION: Does diphenylhydantoin sodium ("dilantin") affect the electroencephalogram?

DR. M. A. PERLSTEIN, Chicago: No. Normal electroencephalograms may be obtained from persons with grand mal epilepsy, the type in which interseizure patterns may be absent. In fact, in about 10 per cent of persons with convulsions, the electroencephalogram may be normal. If records are made while these persons are asleep, abnormalities may appear that were absent from the waking records. Thus, a normal encephalogram does not mean that the patient does not have epilepsy.

QUESTION: Does diphenylhydantoin sodium ("dilantin") affect the electroencephalogram?

DR. M. A. PERLSTEIN, Chicago: Not too much. The slight amount of change effected by the drug is surprising in view of the dramatic clinical improvement. This observation is true of phenobarbital also; in fact, the only drug whose clinical effect is recorded in the encephalogram is trimethadione, which may entirely inhibit the petit mal waves in the electroencephalogram. I should like to

ask Dr. Putnam what his experience with the electroencephalograms of patients receiving diphenylhydantoin sodium has been.

DR. T. J. PUTNAM, Beverly Hills, Calif.: My experience has been essentially the same as that of Dr. Perlstein. The records of some patients have been modified, but this is not the general rule.

QUESTION: What are the electroencephalographic changes in migraine and in Parkinson's syndrome?

DR. M. A. PERLSTEIN, Chicago: Generally, the electroencephalograms are normal since the cortex is not usually involved. Likewise, in a series of children with cerebral palsy of the athetoid type, my colleagues and I observed that 90 per cent had normal electroencephalograms. Apparently, it is necessary for the cortex to be involved, or at least the areas containing connective fibers, before the electroencephalogram is affected.

QUESTION: At what age in infancy or young childhood can one expect to get a satisfactory electroencephalogram?

DR. M. A. PERLSTEIN, Chicago: That depends on who does it. Dr. F. A. Gibbs, who has established normal records for infants and young children, is able to make reliable reports on children as young as 3 months of age. Working with children of this age takes a great deal of experience, however, and should not be attempted by the novice.

QUESTION: Should a child with epilepsy be allowed to attend regular school?

DR. M. G. PETERMAN, Milwaukee: It depends on the number of seizures. If the seizures occur only once or twice a year, it would be well to take the chance and let him go. If they occur frequently, it would be better to put the child in a small school, particularly, a school not attended by friends and neighbors. A child will have fewer seizures when away from his natural environment than when he is associated with the family and neighbors.

QUESTION: How long must a ketogenic diet be maintained in order reasonably to expect "permanent" relief from epileptic seizures?

DR. M. G. PETERMAN, Milwaukee: Usually, it is maintained rather strictly for a year, and no changes are made for three or four months after the last seizure, then changes are made gradually. At the end of a year after the last seizure, the patient is on a fairly normal diet. If the ketogenic diet will be effective, in most cases it is effective within six months. If no great improvement occurs in six months, the diet may well be discontinued.

QUESTION: What are the differences between phenobarbital, "luminal" and N-methyl phenobarbital ("mebaral")?

DR. M. G. PETERMAN, Milwaukee: The differences are mostly in the price and the manufacturer.

QUESTION: Does the new drug "thyphentoin" have any effect on nervous tic?

DR. M. G. PETERMAN, Milwaukee: None whatever. I tried it in true cases and observed no result.

QUESTION: How long should a child with epilepsy be treated after his seizures are under control?

DR. M. G. PETERMAN, Milwaukee: For at least one year and then perhaps for another year.

QUESTION: Why have several physicians, such as Helmholz, stated that diphenylhydantoin sodium was more effective than any other drug in the treatment of petit mal, when you and Lennox state that diphenylhydantoin sodium has no effect whatever on petit mal seizures?

DR. M. G. PETERMAN, Milwaukee: That is one of the mysteries of medicine. It is difficult to understand, and has been for many years, why diphenylhydantoin sodium was reported as a drug useful in the treatment of petit mal epilepsy in children until Lennox suddenly came out against its use. I have obtained no positive results with diphenylhydantoin sodium in petit mal.

QUESTION: What is the latest report on the largest series of cases treated with ketogenic diet?

DR. M. G. PETERMAN, Milwaukee: That would be Keith's report (*Proc. Staff Meet., Mayo Clin.* **22**:14 [Jan. 8] 1947).

QUESTION: Dr. Hoyne, what are the criteria for using penicillin and the sulfonamide compounds in pneumococcic meningitis?

DR. A. L. HOYNE, Chicago: The results of my colleagues and me with intrathecal administration of penicillin have been disappointing. Although the spinal fluid often is readily cleared of organisms, we have had a number of relapses with disastrous results. All our patients with pneumococcic meningitis receive penicillin intramuscularly until the temperature is normal.

QUESTION: Have you seen many cases of aphasia following meningitis?

DR. A. L. HOYNE, Chicago: We have had a few cases develop after the patient's discharge following what was thought to be a complete recovery.

QUESTION: How often have you seen deafness occur which was attributable to streptomycin therapy?

DR. A. L. HOYNE, Chicago: We have had only 1 patient given treatment with streptomycin in whom deafness developed. Some cases of apparent deafness occurred in infants in whom it was difficult to determine whether the child was deaf or not. Deafness may develop soon after the onset of meningitis and bear no relation to streptomycin therapy.

QUESTION: Do you believe that blocks are frequent when penicillin is given intrathecally?

DR. A. L. HOYNE, Chicago: I have seen no blocks, perhaps because I seldom use this form of treatment. However, it seems that blocks are being reported with increasing frequency.

QUESTION: Do you think type B anti-influenza serum should be used for all children with influenzal meningitis?

DR. A. L. HOYNE, Chicago: I believe that type B anti-influenza serum is rarely required if streptomycin is available. However, to infants under 6 months of age I should probably give anti-influenza serum as well as streptomycin. Some patients treated with a sulfonamide drug will recover, although they receive neither streptomycin nor serum.

QUESTION: What has been your experience with regard to local reactions following the use of streptomycin?

DR. A. L. HOYNE, Chicago: In a good many patients considerable induration developed after the intramuscular use of streptomycin, but few had any systemic reactions.

QUESTION: Dr. Ratner, what is the percentage of eosinophils in persons with an allergy, and what is its significance?

DR. BRET RATNER, New York: I confess I did not understand the question too well. It is always easy to talk about eosinophilia because so little is known about it. One thought that I should like to leave with you about eosinophilia is that, actually, its relation to allergy is not known. However, it is significant that eosinophilia is never present in a person with an acute allergy. Eosinophilia is never seen in serum sickness or in early allergic manifestations. Eosinophilia denotes chronicity. If eosinophilia is used as a criterion, as a lead to the direction of the allergy, it will not apply in acute conditions. It occurs only in persons with chronic allergy.

QUESTION: What about allergies manifested as peripheral neuritis?

DR. BRET RATNER, New York: Peripheral neuritis is an extremely important condition, perhaps the most important condition occurring as the result of injections of serum. It is an interesting condition because the child who gets vaccines and antitoxins may have a peripheral paralysis that may last for many weeks, perhaps, many months. It is fortunate that the prognosis is good. I have had 1 such case which assumed medicolegal proportions. The child had been to a camp, which was sued by the parents because the paralysis resulted from an injection of tetanus antitoxin. It was shown that the neuritis was the result of the tetanus antitoxin, that the condition was due to no fault of the physician and that no indiscretion existed.

QUESTION: Can allergy and epilepsy coexist? Would you treat each separately?

DR. BRET RATNER, New York: I should send the patient to Dr. Peterman for treatment of the epileptic phase, and I would treat the allergic phases.

QUESTION: Does the anoxemia of asthma produce convulsions?

DR. BRET RATNER, New York: That is a very interesting question. Many years ago, when a prominent physician in the field of anaphylaxis in France, Besredka assumed that all anaphylaxis was neurogenic. He suggested that if anaphylactic tests were done the injections should be made into the brain or spinal canal. It is now known that the anaphylactic phenomenon observed in guinea pigs or in the human subject can result in convulsions, which should be attributed to anoxia.

QUESTION: Is anticonvulsant therapy over a long period recommended after a simple convulsion from an infection, such as one of the upper respiratory tract?

DR. J. A. TOOMEY, Cleveland: The answer is no.

QUESTION: Has tetanus antitoxin any value for prophylactic use?

DR. J. A. TOOMEY, Cleveland: In my opinion, it must be used but its merit is doubtful. If the convulsions and spasms in tetanus itself are controlled, the patient can be controlled. Whether tetanus antitoxin should be given is debatable.

QUESTION: Has not the reduction in the incidence of convulsions been due to the reduction in the incidence of rickets?

DR. J. A. TOOMEY, Cleveland: I do not believe so. A late issue of *The Journal of the American Medical Association* stated that many children are rachitic, even in the South where there is plenty of sunshine.

QUESTION: What has been your experience with streptomycin in the treatment of tuberculous meningitis?

DR. J. A. TOOMEY, Cleveland: My colleagues and I have seen 4 cases. One child 5 years of age had miliary tuberculosis. This child had proved tuberculous meningitis. After two months the meningitis subsided. The roentgenographic picture of the lung remained about the same. I saw a patient in Los Angeles a month or so ago with miliary tuberculosis of the chest and tuberculous meningitis. He had received early treatment, and he recovered. We have 2 patients who were treated with streptomycin, and they are still living. Whether or not their meningitis will clear up completely, I do not know. Streptomycin has a definite effect on the tubercle bacilli.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Dr. H. William Elghammer, *President*

Regular Meeting, Oct. 14, 1947

BCG Vaccination Program in Chicago. Dr. Robert A. Black.

In 1933, Dr. Frederick Tice, president of the board of the City of Chicago Municipal Tuberculosis Sanitarium, conceived the idea of having BCG introduced into Chicago. He asked Dr. Sol Roy Rosenthal to study the problem at the Institute Pasteur in Paris, France. When Dr. Rosenthal completed his studies there, he brought back cultures and set up a laboratory at the University of Illinois for a reevaluation of the safety of the vaccine on an experimental basis. Three years of such study on thousands of animals definitely established the fact that the bacillus of Calmette and Guérin failed to produce progressive tuberculosis. When the question of vaccinating human subjects was considered, a committee was appointed in 1936 by the mayor of Chicago to evaluate the problem. The plan of procedure, as presented to the committee by Dr. Rosenthal, was as follows: The vaccine would be assayed continuously in animals to insure its safety. A control group which in every way simulated the vaccinated group was to be studied; this differed from the procedure in most of the experiments up to that time. The study was to be made at Cook County Hospital, beginning in the prenatal clinic. Only those cases would be accepted for study in which roentgenograms of the chest of every member of the household were negative for tuberculosis.

The committee has met more or less on a yearly basis to review results for the past year and to make recommendations; it has now been functioning eleven years. Up to the present, plans of procedure for vaccination of the following groups have been recommended: (1) newborn infants in nontuberculous households; (2) newborn infants in tuberculous households with isolation in foster homes after vaccination; (3) nursing students; (4) medical students; (5) children of all age groups in two government housing projects and in two orphanages, and (6) inmates of Manteno State Hospital.

From the results of the program as carried out thus far it can be said that BCG vaccination is absolutely safe and that it prevents, to a certain extent, the development of primary virulent tuberculosis and of the primary progressive phase of the disease.

It is felt that vaccination of newborn infants is the most economical and efficient approach. The Chicago Department of Health and the infant welfare organizations should have a joint program. Regularly scheduled visits should be made to maternity wards of hospitals frequented by persons from highly infected districts. All mothers should have a roentgenographic examination of the chest. Vaccination is to be made after the third day of life for normal infants; controls are to be determined by local authorities. Follow-up studies can be carried on through infant welfare societies and clinics. Tuberculin patch tests can be made in the field and followed through from the records of infant welfare organizations. After this program is established, first year grammar and high school

students need be contacted only once yearly. Vaccination of newborn infants, however, would be continued as outlined.

It is recommended for the present that BCG vaccination be carried on only in that portion of the population most susceptible to tuberculosis and in districts where the incidence of infection is unduly high.

Laboratory and Technical Aspects of BCG Vaccination. DR. SOL ROY ROSENTHAL.

In a report by the United States Public Health Service, as well as in one made for the British government, it was agreed that BCG should be produced in a central laboratory to afford a standard method of comparison, to combat the fastness of the organism, to guarantee the minute care necessary in the production of the vaccine, as the final product is a living organism to which no preservative can be added, and to insure extremely careful determination of its virulence.

The calamities that have been reported in the literature can be avoided by establishment of a central laboratory whose sole function is the production and assay of BCG.

The method used in culturing the organism is that of the Institute Pasteur, Paris, France. At no time over a thirteen year period, in which thousands of animals (guinea pigs and rabbits) were vaccinated has the Chicago group of workers ever noted progressive tuberculosis. Sterility studies, as well as viability studies, are made on every batch of vaccine. It can readily be understood that for a method of vaccination to become universally popular complications must be at a minimum. For this reason the method of scarification by multiple puncture was developed by the Tice Laboratories. The technic is described.

With this method, complications have practically disappeared. After the vaccination, almost every person (99.7 per cent) reacts to tuberculin in four to six weeks. The duration of the reaction to tuberculin following a single vaccination after six and a half years is almost 80 per cent. This method has been adopted in France, Norway and several of the South American countries.

It is concluded that the recommendation for the establishment of a central laboratory for production of BCG, as discussed by the United States Public Health Service and by the Prophit Survey for the British government, is substantiated and that scarification by multiple puncture is considered the method of choice for administration of the vaccine.

Ten Public Health Aspects of BCG Vaccination. DR. ANDREW C. IVY.

I have been associated with the BCG program during the last year as an administrator. When I went to the University of Illinois as vice president in charge of the Chicago Professional Colleges, I was confronted with a request that increased space be provided for the production of BCG vaccine and for research on the prevention of tuberculosis. In an investigation of the evidence in favor of such a development, I found that Dr. Tice was to be congratulated for starting a research project on the vaccine in Chicago some thirteen years ago, and that Dr. Rosenthal was to be congratulated for his perseverance and for the great care with which he has conducted the study. The mayor's committee must also be commended, for its members have constantly supervised the work during the past thirteen years.

After my study of the evidence, I came to the conclusion that the vaccine, when produced under carefully controlled conditions, is safe and that, when the multiple puncture method of vaccination is used, no complications occur. Furthermore, I was convinced that if the patient has a negative reaction to tuberculin

no reaction to BCG occurs, but a reaction to the vaccine may occur if the patient has even a slightly positive reaction to tuberculin. For that reason, Dr. Rosenthal, in my opinion, was correct in refusing to vaccinate anyone with even a slightly positive reaction to tuberculin. This action prevented his vaccination program from being destructively criticized and receiving a setback. I reached the final conclusion that BCG vaccination should be fostered as a program of clinical investigation, since it now appears to constitute an important step toward the prevention of tuberculosis.

In the past, we have depended solely on the isolation of tuberculous patients and the treatment of contacts. More recently, emphasis was placed on the detection of contacts. This program led to the construction of hospitals with more and more beds for tuberculous patients. It is time something was done to prevent tuberculosis, something other than the difficult and expensive method of discovering, isolating and treating contacts. Some such way must be devised to prevent tuberculosis as was found for smallpox, diphtheria and certain other diseases formerly treated also with isolation in a hospital for contagious diseases.

It should be emphasized that tuberculosis is a chronic disease and that much more time will be required to evaluate a program of vaccination against tuberculosis than will be required to evaluate a program against an acute disease such as smallpox and diphtheria, or even typhoid and pneumonia. Much patience, care and perseverance will be required. For these reasons, I feel that Dr. Tice and Dr. Rosenthal and the mayor's committee deserve congratulations for initiating the study and for continuing it until they have produced evidence which, in my opinion, unequivocally shows that BCG vaccine, when properly prepared, is harmless. They have also shown that when the subjects are properly vaccinated the vaccine does not produce harmful reactions and their observations to date indicate that the vaccine is effective in the prevention of tuberculosis. Of course, it is fully realized that more evidence is required to substantiate this last point.

By fostering and furthering work of this sort we can, in time, greatly reduce the need for sanatoriums for patients with tuberculosis. At present, BCG vaccination should not be considered as detracting from the emphasis on detection, isolation and treatment of contacts or from the necessity for improvement in the treatment of patients who already have tuberculosis. We should look on vaccination as a means of greatly reducing the incidence of the disease in the population in the next twenty to forty years or, it is hoped, even sooner, If we cannot effect that reduction with BCG vaccination, then let us pursue this line of attack until we do have a successful vaccine against tuberculosis.

DISCUSSION

DR. EUGENE T. MCENERY: Dr. Black and Dr. Rosenthal are to be congratulated on their BCG program. Every safeguard has been taken to avoid serious complications following the use of the vaccine and to prevent the unfortunate disasters that occurred when proper precautions were not taken. Certainly, the work should be carried out by a public health organization, not by the individual practitioner. If the program is carried on through well organized clinics, BCG immunization will not be blamed for many things for which it is not responsible.

One may ask exactly what happens when BCG vaccination is performed. Does it produce an immunity or an allergic response? How long does this so-called immunity last? It may take many years to answer these questions, and the work should be carefully followed through many years—fifteen, fifty or even a hundred years.

A primary infection is the result of the implantation of tubercle bacillus (Mycobacterium tuberculosis) in the terminal alveoli of the lung. This bacillus sets up an inflammatory reaction which spreads along the lymphatic glands to glands at the hilus, and in three to six months calcification appears. This process constitutes the primary complex. If a child is vaccinated with BCG on the arm, the reaction is localized about the site of the vaccination and the axillary glands become swollen. No shadows are produced on roentgenogram of the pulmonary fields. How can one tell whether a primary infection has developed in the child? Where is the infection, and how can its progress be followed? The primary infection in the child is usually benign. What happens when the child reaches adolescence, when the child becomes reinfected or when the primary lesion breaks down? Adolescents seem to have little resistance to this type of infection, and we wonder whether they may have been sensitized by an early primary infection.

Before BCG is released for general use, the program should be worked out thoroughly and studied for a long time.

DR. HENRY C. SWEANY: I have had no experience with BCG, and my opinion of it has been formed by what I have read and observed. In 1928 I was asked to handle the BCG program which Dr. Julius H. Hess initiated and which Dr. Benjamin Goldberg attempted to carry out in this country, but because of the adverse reports it was decided not to continue the work at that time. Later, as you have heard, Dr. Tice and Dr. Rosenthal revived the plan, and the work is now being carried on with all precautions to protect the public from any errors such as occurred in Lübeck, Germany.

Everyone will concede at this time that BCG vaccination is harmless, although that fact was not conceded at first. It will give a slight amount of protection to any vaccinated person. That statement may be doubted by a few workers, but not many will question the fact that BCG vaccination will raise the threshold of infectability above that of the nonvaccinated person.

We do not know how long the protection lasts. No one can say whether it disappears with the cutaneous reaction; nor has it been possible to measure the exact amount of protection conferred. The tubercle bacillus will infect anyone at any time if a large enough dose is given, and we do not know the largest dose of tubercle bacilli against which BCG will offer protection.

I am in a neutral position with regard to the use of BCG. There may be certain indications that it is definitely of benefit and certain places where it may do great good. For example, in war-torn countries where public health agencies have broken down, it could be used to advantage, as well as in countries where the infection rate is high and the public health service is not effective. However, there is always the danger of causing false overtrust. Persons may think this protective vaccination will accomplish all that can be done by regular public health agencies. Danger, therefore, lies in using this shorter and cheaper method when it is not the best way and will not solve the problem alone; government financial experts also may be misled by the "cheaper" way. The best plan still is to remove contacts and to carry out public health work as has been so well done in many municipalities by the regular public health measures. BCG may be used as a supportive measure, but not to the exclusion of other measures.

BCG causes a positive reaction to tuberculin. In many instances it is important to know whether a person has a negative reaction to tuberculin. Such knowledge is useful in tracking infection to its source. The utility of this practice will become decidedly limited because BCG makes the reactions of all subjects positive. A negative reaction to tuberculin is of great aid in arriving at a diagnosis in a questionable condition involving the chest. Since 30 to 50 per cent of adults

now have negative reactions, and the percentage is rising, the value of a negative reaction becomes increasingly more apparent. To have the reactions of these people rendered positive confuses the picture and the diagnosis.

There are reasons, then, for not using BCG except under special circumstances, as previously mentioned. Undoubtedly, the greatest use for it at this time is for medical students, attendants and nurses who care for tuberculous patients. Perhaps we should hesitate to go beyond that group at present. We should keep in mind that it is still an experimental vaccination. I doubt that we can claim that it is a proved and well established method for widespread public use. There is, however, a splendid opportunity in France for a study of those subjects vaccinated twenty years ago. The incidence of tuberculosis for the vaccinated persons should be compared with that for persons in the same age group who were not vaccinated. This study would give us an idea of the true value of the vaccine as a further public health weapon.

DR. JOHN A. BIGLER, Highland Park, Ill.: Most physicians have had no experience with BCG vaccination. The technic of immunization is not so simple as it may seem. When a child is to be immunized with BCG, studies must be made of the family and of all contacts of the child, as well as of the child himself. The possibility of the presence of tuberculosis in the family and contacts must be eliminated by negative reactions to tuberculin tests, as well as by negative roentgenographic findings. Then the child, if not in the newborn period, must himself have a negative reaction to tuberculin in dilution of at least 1:100 before vaccination can be done.

If there is any contact in the family group with possible active tuberculosis, the child must be removed from the family for at least six weeks before vaccination can be attempted, and he must be away from such contact for at least six weeks after vaccination. This is a long time to have a child out of the family, and at present it is difficult to find placement for such a child for that period of time.

It is usually difficult to convince the family of the wisdom of such a program. One is also faced with the variability of the criteria by which the roentgenographic diagnosis of tuberculosis is made among various roentgenologists.

The setup for BCG vaccination, other than in the newborn period, would have to be fairly elaborate and expensive. I hope that in the near future a clinic can be developed for such a program with the expense carried by some agency, so that a noninfected child coming from an infected family may have the benefit of this protection.

DR. ELEANOR I. LESLIE, Evanston, Ill.: During my work in the Tice Clinic I have been impressed with the care taken to have both the control groups and the vaccinated groups as nearly similar as possible; no discrimination is made. Prophylactic work, hygiene and attempts to teach parents are emphasized in both groups.

I should like to mention the nature of the lesions encountered. Among the subjects of the noncontact series in which no known tuberculosis exists in the family, 1 death from tuberculosis occurred in a child of poor parentage in the vaccinated group, while 7 deaths from tuberculosis occurred in the nonvaccinated group. The vaccinated child died at the age of 2 years. In the nonvaccinated group, 3 children died before the age of 1½ years, 3 before the age of 3, and 1 at the age of 8. In all but 1 of the children who died, the tuberculosis was of the meningeal form resulting from a general spread. In the 11 vaccinated children, except for the 1 who died, the tuberculosis was of relatively milder type, without extensive spread, and the lesions that did develop seemed to clear more rapidly

than those which developed in the control group. In the 11 nonvaccinated children, those who survived had roentgenographic evidence of tuberculosis lasting eighteen months or more, whereas in the vaccinated group roentgenograms were clear after twelve months.

In the contact series, there have been no deaths from tuberculosis among the vaccinated children and 4 deaths among the nonvaccinated children. Two cases of tuberculosis, however, occurred in the vaccinated children in the contact group. One case was merely a tuberculous calcification; the other was a hilar infiltration which cleared up within twelve months. In the nonvaccinated children in this group, 2 under 1 year of age died of tuberculous meningitis, and 2 others died at about the age of 3. In 1 child tuberculosis developed at 1 year of age, and the lesion persisted for three years before roentgenograms showed that healing was beginning to take place.

DR. NORTH (director, Serum Laboratory), Melbourne, Australia: Dr. Sweany mentioned that one of the disadvantages of BCG is that it may lead to possible confusion in diagnosis later on because it produces a positive reaction to tuberculin. I have been in the Scandinavian countries during the past six months, and it was pointed out to me that the reaction to the Mantoux test resulting from BCG vaccination is quite different from the reaction to the Mantoux test which is the result of a natural infection. With BCG the area of infiltration is definitely diametric and erythemic in the reaction resulting from a natural infection, but in the typical Mantoux reaction to natural infection the central area of infiltration seems flatter, with more defects, and the disclosed area instead of being bright seems blurred. One of the interesting studies in Norway—and the physician was actually doing it statistically, as he felt interesting results would be obtained from this analysis of figures—was on the gradual transition in some cases from the reaction following BCG vaccination to the typical Mantoux reaction noted in a natural infection.

DR. C. E. STEPAN: It is possible that many of the persons inoculated would not know in twenty years whether or not they had been vaccinated. It would seem that some identification should be marked on the body so that it would be known that they had been vaccinated. Dr. Rosenthal mentioned one such procedure, and I suggest that something of this type be standardized throughout the country.

DR. SOL ROY ROSENTHAL: Our major premise in BCG vaccination is to use it as a method complementing the already existing time-proved procedures in prevention of tuberculosis, such as the discovery of the source cases and the isolation of them. These are the procedures used for other diseases in which vaccination is practiced. We should not expect more of BCG vaccination than we do of diphtheria, typhoid or smallpox vaccination. The isolation of the source case is paramount in control of the disease.

In Dr. Turner's discussion of the work of Dr. Jay Arthur Myers, of Milwaukee, not enough emphasis was placed on the fact that only after nursing students were not allowed to go on a tuberculosis service did the percentage of reactors to tuberculin remain constant. It was not the contagious technic they used, for this technic has been followed at Wisconsin General Hospital in Madison, Wis., and at Cook County Hospital in Chicago without striking success. In fact, the reason the tuberculosis service was discontinued in the nursing schools, as reported by Dr. Myers, was because of the high incidence of tuberculosis in the negative reactors as compared with the positive reactors.

No one will deny that if a person does not come in contact with the causative organism he will not contact the disease. If it were possible to isolate every member of a community who has tuberculosis at the instant the disease develops, tuberculosis could be controlled, but, in a city like Chicago, for example, that is impossible. In 95 per cent of all cases of tuberculosis reported in Chicago there is no known history of contact.

In regard to the loss of the tuberculin test as a method of diagnosis, it must be said that in the final analysis only the roentgenogram determines the presence of a clinical pulmonary disase. Dr. Leslie and I have gone over thousands of roentgenograms of children showing positive reactions to tuberculin, and we have not deemed it necessary to isolate a child on the strength of merely the tuberculin test. We have followed such children for as long as ten years.

Does BCG produce immunity? Our results, as well as those of other workers all over the world, indicate definitely that it does. As to the duration of immunity after vaccination, in one roentgenographic study in France made eighteen years after vaccination, it was reported by Dr. B. Weill-Hallé that the vaccinated person showed about one-fourth as much calcification as the controls. Our statistics indicate that one vaccination should last from four to six years.

With reference to Dr. Bigler's comment, we do not feel that it is necessary to run as strictly controlled groups as at the Tice Clinic. We should recommend for the vaccination of children, for example, that they be tested with tuberculin in the schools. All negative reactors should then be vaccinated. We should ascertain from our tuberculosis dispensaries the list of active cases and exclude from vaccination children from households in which active tuberculosis is present, unless the children can be isolated for six weeks before and after vaccination.

As for identification of those vaccinated, we should recommend tattooing, such as we already have done to the inmates of the Manteno State Hospital.

I wish to stress the fact that everyone agrees now that BCG is safe. All reports thus far indicate that a certain degree of protection is afforded following vaccination. I recommend that the use of BCG vaccine complement the already existing methods of control of tuberculosis.

Book Reviews

Subdural Hematoma in Infants. By Juan F. Cassinelli and Rodolfo E. Tiscornia. Pp. 90. Published by the authors in Montevideo, Uraguay, 1947.

This is a review of the literature on the subject, with a detailed presentation of 3 cases. The monograph is interesting in the presentation of several roentgenograms taken after injection of air into the subdural space after the blood had been evacuated. This technic gives the delineation of the hematoma.

In 2 of the cases presented, punctures of the superior sagittal sinus for withdrawal of blood had been made. While the authors presented evidence that this did not contribute to the cause of the hematoma, it still seems to the reviewer that sinus puncture is an unnecessary and potentially dangerous procedure.

The anatomic nature of the lesion is particularly well discussed, with clarification of the confusion existing in many minds as to the exact location of the hemorrhage. The book is recommended to all those who are especially interested in the subject.

Physiology of Man in the Desert. By E. F. Adolph and others. Price $6.50. Pp. 357. New York: Interscience Publishers, 1947.

This work was done under a contract, recommended by the Committee on Medical Research, between the United States Office of Scientific Research and Development and the University of Rochester School of Medicine and Dentistry. It represents a large scale investigation in the field of environmental physiology from 1942 to 1945 and was conducted by a group of physiologists known as the Rochester Desert Union. It was done under the leadership of E. F. Adolph and a group of his associates. A greater part of their studies were made at the camp at Blythe, Calif., which is in the heart of the desert of southern California in the lower Colorado Basin.

Studies were made on soldiers, who volunteered for the tests. Men made long hikes in the blazing sun in temperatures ranging from 100 to 120, and were weighed every hour to estimate the sweat loss; the amount of water they drank was weighed and measured. During some of the hikes they were given all the water they wanted, while during others they were given small amounts of water in an attempt to estimate how long a man could go without water. Experiments on the chewing of gum to keep the mouth moist were tried. Ice was used to keep the mouth cool, but it was found that there is no substitute for water. Estimates were made of perspiration loss. It was found that when the outside heat is greater than the body temperature clothing helps to keep the heat out. On some of these hikes men lost as much as 11 per cent of their weight in perspiration. The investigators found that shade enabled men to stand much higher temperatures, and they advise that a canopy be carried by people traveling across the desert so that a shade can be thrown up if they have to stop. Traveling at night was much more satisfactory and could be done with much less loss of body weight and physical exhaustion. Many of the hikes continued until the men began to drop with exhaustion. When this happened, the investigators estimated the

weight loss, the pulse rate and the body temperature. The subjects, of course, were soldiers who were in fit condition.

It was found that men who lose from 1 to 11 per cent of their body weight by sweating show a loss in volume of circulating plasma about two and a half times as great as the corresponding loss in weight. The increases in concentration of chloride, urea or nitrogen during rapid dehydration are no greater than would be expected from the depletion of water. The sugar concentration, however, increases more than would be expected, serum concentrations are promptly restored when plenty of water is given and the redistribution of water is as rapid as is absorption from the alimentary tract. These experiments were also checked in a chamber in which the heat and humidity could be controlled. The investigators studied the rodents of the desert. These rodents live far underground, and many of them require no water at all, getting moisture from the succulent foods they eat. If they were fed strictly dry diet, they would take water, but if they were fed succulent foods, which they preferred, they took no water. The syndrome of dehydration is described, and the length of time which is required for recovery from desert exhaustion is given.

This book will prove interesting to anyone interested in physiologic studies. The reviewer has lived for over forty years in arid or semiarid country and is aware that the methods described for sustaining life in the desert are practiced by the aborigines who have lived there for many, many generations.

Illustrative Electrocardiography. By Julius Burnstein and Nathan Bloom. Third edition. Price $6. Pp. 325. New York: D. Appleton-Century Company, 1948.

This is an excellent book for students who are beginning the study of electrocardiography. The authors describe in simple terms the form of the normal electrocardiogram and illustrate the classic deviations from the normal. The illustrations are well selected and accompanied with adequate and concise explanations. The arrangement and form make it an easy textbook to follow. The print is clearcut and easily read.

The book includes a brief but excellent discussion of precordial leads but is rather lacking in illustrations of the abnormal patterns found in these leads. There is little concerning the variations of the electrocardiogram in children. The authors have included some illustrations of phonocardiograms and cardiovascular silhouettes which, while not essential to a book on electrocardiography, are of general interest to the student of cardiology.

The authors state in the preface that they have avoided the theoretic aspects of electrocardiography. Although this does serve to make the book easier to read and adequate for the beginner, it does not satisfy the specialist. The specialist will also be disappointed at not finding more complete coverage of the many possible variations in the electrocardiographic complexes. The more unusual aspects of the electrocardiographic abnormalities are given little attention. The book lacks a bibliography, which somewhat detracts from its value as a textbook.

How to Help Your Child Grow Up. By Angelo Patri. Price $4. Pp. 360. Chicago: Rand McNally, Publishers, 1948.

The material in this book is an adaptation of the material used in "Our Children," which is a newspaper column.

The material is divided into seven parts and forty-eight subtopics. The seven parts are "The Child Himself," "The Baby," "The Child at Home," "The Child in the Neighborhood," "The Child at School," "Growing into Youth," and "Sug-

gestions for Special Problems." The subtitles deal with such subjects as "The Baby in the Family" and states: "A baby can make or break a family according to the training he gets." For the most part the book deals with everyday problems of the school age child. The author stresses the need for a kindly but persistent attempt on the part of parents to train children to be honorable and good.

The author was originally the principal of a school. His approach is that of the good educator of twenty-five years ago. The book contains little or none of the scientific principles of growth and development and little of the advances in progressive education, child psychology, pediatrics or psychiatry.

The discussions are superficial and do not include underlying causes of behavior.

Year Book of Pediatrics. Edited by Isaac A. Abt, M.D. Price $3.75. Pp. 454. Chicago: Year Book Publishers, Inc., 1947.

Dr. Isaac A. Abt and Arthur F. Abt have been editing these useful little volumes for forty-six years. The book has constantly increased in value, and the present edition is one of the best. As usual, the book is a gold mine of information. Abstracts are uniformly clear, concise and adequate. Editorial comments are infrequent and, to this reviewer, do not seem particularly informative.

To the busy practitioner, these year books are an invaluable aid in keeping up with the vast amount of pediatric literature published. He who reads the "Year Book of Pediatrics" regularly will never be found lacking in knowledge of current developments.

Nursing in Modern Society. By Mary Ella Chayer, R.N., M.A. Price $4. Pp. 288. New York: G. J. Putnam's Sons, 1947.

With emphasis on the acknowledgment that we are living in a world of changing thought, the author points out the development of nursing since the days of Florence Nightingale, including the industrial revolution, the changing status of women in society and changes in population. Health legislation such as the Social Security Act, the Emergency Maternal and Infant Care Plan and the Wagner-Murray-Dingell bill has influenced nursing as a profession and in many ways altered its course of endeavor but yet has produced one of the greatest challenges that has ever come to the women of modern society. The subject is well coverd and written in a straightforward inspirational style which sets the nursing profession apart as one of the greatest social forces in the modern world. The potency of the author's work, which includes a statement of the problems of the nursing profession, the possibilities of solving these problems and stimulating questions for study, is so great that this book could be used advantageously not only by nurses but by any student group concentrating on the health progress of family, school or community.

The widening concepts of public health in meeting the changing picture of community needs brought about by advances of medical science, newer knowledge of nutrition and of child development, economics of the family and a deeper concern for the individual are pointed out as a great challenge to the nursing profession as well as to communities as a whole. Recognizing that the nursing profession and the public are beginning to realize "the need for a better understanding of human behavior and for better care of those who are suffering from personality disorders; that the confusion into which parents and health workers have been plunged with reference to child care and training is being clarified; that the right and dignity of parenthood among all classes is reasserting itself; and that adults

in our fast-aging population have a right to enjoy the fruits of medical science during their advancing years," the author goes further and outlines, discusses and summarizes in a concise manner methods by which these problems may be approached.

The outstanding means of solving present day health problems is indicated as being the promise of health education. The author clearly defines and states principles of health education, recognizes all contributors participating in its programs and points out its weaknesses and its future trends as well as the means of fulfilling its promise.

The unity of all nurses in one official national administrative organization instead of six is charted as one of the important steps in solving the problems of the nursing profession. The awareness of nursing to new demands presents a problem for much consideration in the so-called nursing shortage. An evaluation of the progress and responsibility of nursing as a social force in modern society, in which its entire structure of service and education is reexamined and its purposes and methods are redefined by the author, gives promise of a greater nursing profession in the future for this country and for the world at large.

Handbook of Child Guidance. Edited by Ernest Harms. Price $8.60. Pp. 751. New York: Child Care Publications, 1947.

This book deals with all phases of child guidance, and although it is perhaps a bit lengthy and detailed to be consulted for the ordinary problems of pediatric practice, it should be of great value for reference in particular cases. Those especially interested in mental hygiene, its practical application and the present concept that it must be an integral part of any adequate educational program will find the book most useful indeed. It should be read by educators in the nursery school, the secondary school and even the university and graduate school. As stated by the editor in his preface, "It is thus the aim of this volume to set forth in the broadest sense the theory and practice of child guidance for the normal as well as for the subnormal child."

Each phase of child guidance is covered by a contributor with experience in the particular field, and in general each chapter is well done. The repetition and overlapping are more or less unavoidable in such a volume.

The book is divided into eight parts. Part 1 is a short résumé of the development of child guidance in the United States. Part 2 treats the guidance of the normal child from nursery school age through secondary school. The chapters on the adolescent, the superior child and the prodigy are especially interesting.

Part 3 concerns guidance of the physically handicapped child. Part 4 covers guidance of the problem child and the subnormal child. The pediatrician will find these two sections of great help in understanding, evaluating and solving many of the problems encountered in his own practice and those referred to him.

Part 5, entitled "Training for Child Guidance," contains suggestions for the training of the physician, the psychiatrist, the psychologist and the social worker in child guidance. Anyone engaged in pediatric teaching will find this section a help in giving students a better understanding of the relationship of mental hygiene and psychiatry to everyday private practice and human behavior.

Part 6 covers the social aspects of child guidance. There are chapters on such phases as the home and the family, city and rural guidance, delinquency, institutional treatment, vocational guidance, camping, guidance problems of Negro children and the special problems of migrant children. This part obviously will be

useful to the social service worker and the public welfare worker and has a practical, common sense approach.

Part 7 is a short section on the religious aspects of child guidance, and part 8 is a presentation of Freud's, Adler's and Jung's viewpoints on child guidance.

Memento de posologie et de therapeutique infantiles. By a committee of the Society of Pediatrics of Paris. Price, 150 fr. Pp. 158. Paris: Doin & Cie and Mason & Cie, 1948.

This little booklet, compiled for practicing physicians by a committee of the Society of Pediatrics of Paris, is an improvement on treatises on posology and therapy in some textbooks as it attempts to indicate dosage for children per se and not in fractions of adult doses, thus permitting consideration of possible differences in the reaction of the growing organism to drugs. Doses are given by one of three methods: by age groups (below 30 months and from 30 months to 15 years), by weight (dosage per kilogram of body weight) and by age (dose per year of age. Unfortunately most doses are given by the first method only and are therefore limited in accuracy considering the wide range of age and weight in the two subdivisions used. The value of the book could be greatly enhanced if the "per kilogram" or the "per year of age" scale would be applied to all drugs or if the present two age groups would be further subdivided. However, additional experimental information might have to be gathered in order to do this. Following the chapter on general posology and therapy are chapters on otorhinolaryngology, ophthalmology and dermatology. Dosages of physical therapeutic agents are treated in a separate chapter, and several pages are devoted to the indications for the use of the hydroclimatic resources of France. The last chapter deals with the general and specific treatment of intoxications.

Source Book of Orthopaedics. By Edgar M. Bick, M.D., F.A.C.S. Second edition. Price, $8. Pp. 496. Baltimore: The Williams & Wilkins Company, 1948.

The title of this work, "Source Book of Orthopaedics," may be faintly misleading. It is not a source book in a contemporary sense but rather a historical documentation covering the development of orthopedic surgery over a period of two thousand years. As such it is packed with information that should be of interest to any physician and particularly to orthopedic surgeons. Many of the early physicians, from Hippocrates to Galen, Hunter and others, possessed amazing powers of observation and description. Ingenious methods of treatment were devised for fractures, scoliosis and other skeletal deformities. The book demonstrates throughout that again and again the medical profession has "rediscovered" diagnoses and treatment that had been clearly recognized one hundred years or so before.

The book has been revised and brought up to date. Part two is divided into chapters covering the various phases of orthopedic surgery, and each chapter includes a complete bibliography which gives ready reference for those interested in detailed procedure.

The book is highly recommended as informative and enjoyable reading for every physician and student interested in traumatic or orthopedic surgery.

The Metabolic Brain Diseases and Their Treatment. By G. Tayleur Stockings, M.D. Pp. 262. Baltimore: The Williams & Wilkins Company, 1947.

Psychiatry, of all branches of medicine, is most in need of a new scientific approach. It requires a factual study based on established fundamental anatomic,

physiologic and psychologic principles, with reasonable deductions supported by accurate observations which can be duplicated by any intelligent, observant student of the problem. A psychiatric thesis which finds expression in the quicksands of an obscure and often vague and indefinite terminology, in which the relatively few observations (and those largely subjective) are susceptible of many interpretations depending on the particular bias of the interpreter whose concepts are open and understandable only to the "initiated" can never lead to a sound understanding of mental processes and mental disorders. The necessary scientific approach to the problems of psychiatry is not easy to achieve, nor has it as yet been forthcoming. Anything approaching a real understanding of mental disease still lies in the unforseeable future.

Unfortunately this pseudoscientific monograph, which presumes to point the way to the solution of these problems, does nothing but add to the existing confusion. The author has exhibited no evidence of a true concept of the scientific approach to the study either of normal function or of disease. Although he decries the existing unsatisfactory terminology and confusing verbiage which largely serves only to confuse psychiatric thinking, he has done nothing but add to it. He proposes to explain much psychiatric disease on a disturbance of the metabolic activity of the brain. He admits (page 30) that the presumed metabolic changes have not been demonstrated but waves that fact aside as insignificant by asserting that the changes are probably too slight to be detectable. He also presents (page 29) the rather startling conclusion that as these changes are probably confined to the cerebral cortex and to the "corticodiencephalic and thalamic" connections, to the exclusion of the midbrain, the cerebellum and the medullary nuclei, one can understand the "absence of a characteristic neurological syndrome in association with the mental symptoms." Apparently in his scheme of neurophysiology the cerebral cortex, the thalamus and the hypothalamus have no neurologic function but only a psychologic one. He has divided the various psychiatric disorders which arise from "metabolic brain disease" into two categories, the "dysoxic" and the "dysglycic." In the first there is a presumed disturbance of cerebral respiration and in the second a disturbance of the metabolism of glucose and glycogen in the brain. The evidence for the designation of any particular psychiatric disorder under either of these categories is not discernible in the confused wording of the book. His thesis is apparently based on "three outstanding new facts," which he states as follows: "First, that all the symptoms and signs, as well as the response to specific treatment, can be explained on the basis of the metabolic hypothesis; second, that two distinct types of metabolic encephalopathy can be distinguished according to their response to anoxia (*metrazol or electro-shock therapy*) and hypoglycemia (*insulin shock therapy*); and thirdly, each of these two main types can be differentiated by a distinct syndrome of clinical symptoms."

Although the author's unfamiliarity with the basic facts of cerebral anatomy and physiology is apparent throughout the book, it is well illustrated by his description of the "cortico-striate tract" as the connection between the frontal cortex and the thalamus or, a few lines farther on, as the connection between the frontal area and the globus pallidus. All students of the subject, if they acknowledged its existence, would define it as the connection of the cerebral cortex with the putamen and the caudate nucleus.

It is unfortunate that in a country woefully short of paper (Great Britain), 262 pages have been wasted on this monograph.

Fundamentals of Immunology. By William C. Boyd, Ph.D. Second edition. Price, $6. Pp. 503, with illustrations. New York: Interscience Publishers, Inc., 1947.

The second edition of this book has adequately brought up to date a first edition addressed principally to medical students and research workers. An attempt has been made to present the fundamentals of immunology in an informative manner to those without any previous schooling in this subject, and within the limitations imposed by the intricacy of the subject matter this attempt succeeds admirably well. Immunologic terminology has been well clarified by the text; the discussion on chemical principles seems to assume somewhat more knowledge on the part of the reader.

The pediatrician cannot but profit from a careful reading of this book, thus clarifying his knowledge of the immunologic principles which govern so many of the problems affecting his management of the diagnosis, prevention and treatment of many diseases of infancy and childhood. There are extensive discussions of the general principles of antigens and antibodies and a lucid application of these principles to various clinical and laboratory phenomena.

A section is devoted to blood grouping and the precautions necessary for transfusion, and there is a brief discussion of the nature and significance of the Rh factor. Other sections are devoted to various laboratory immunologic reactions, the nature of anaphylaxis and allergy and the principles of natural and artificial immunization, and a final section is devoted to laboratory and clinical technic, including a brief exposition of statistical principles.

The most stimulating feature of the book is the concept of the nonhomogeneity of antigens and the possibility of reducing immunologic phenomena into a simple and orderly pattern of chemical behavior.

Each section is followed by an excellent summary, and the text is documented with an extensive bibliography. The index is thoroughly adequate. The reviewer cannot judge the appropriateness of this book as a textbook for medical students, but it is valuable and informative reading for the pediatrician, by whom it should be consulted.

Sexual Behavior in the Human Male. By Alfred C. Kinsey, Wardell B. Pomeroy and Clyde D. Martin. Price, $6. Pp. 804. Philadelphia: W. B. Saunders Company, 1948.

This book is compounded from 1,200 case reports of sexual behavior in midwestern Americans. This is the largest group that has been so studied, and the book marks an attempt at observational science. The social sciences need more of these studies along with studies of other more important and less sensational human activities, such as eating habits, personal hygiene and family behavior.

The authors apparently like to report statistical evidence, and they do a good job; they make little or no attempt to justify or condemn the variations of sexual behavior. They have been able to determine to some degree that sexual habits of the individual are determined by the educational level, age and religious training. They also found that a great number of persons who are addicted to atypical sexual activity have apparently been able to rationalize their behavior and are in no need of psychiatric treatment. Most previous books of this nature have been written by one author who reports only his own sexual activity and assumes that it is normal. One could aptly express this book as a study of what men and boys do wrong.

Child Care Questions and Answers. By the Children's Welfare Federation of New York City. Price $2. Pp. 159. New York: Doubleday & Co., 1948.

This excellent little book presents over 400 questions commonly asked by parents, together with answers formulated by a committee of recognized authorities. It is brief, clear and accurate. The questions are divided into sections listed in a brief table of contents, which makes it easy to find answers to specific questions. All the answers are carefully written, and none are likely to be found controversial. Mothers are likely to find most of their ordinary questions answered here. The book can be recommended as a real help to the new parent.

The Rehabilitation of Speech (Revised edition). By Robert West, Professor of Speech Pathology, University of Wisconsin; Lou Kennedy, Associate Professor of Speech, Louisiana State University, and Anna Carr, Clinical Adviser in Speech, State Teachers College, Milwaukee, with a chapter by Ollie L. Backus, Assistant Professor of Speech, University of Michigan. Price $5. Pp. 647, with 53 illustrations. New York: Harper Brothers, 1947.

The first edition of this comprehensive analysis of speech disorders appeared in 1936 and has since been widely used by clinicians and as a textbook for collgee courses. The present revised edition has been largely rewritten and incorporates some of the extremely valuable knowledge and experience which came out of the rehabilitation centers for army and navy personnel in World War II.

The volume is conveniently subdivided into several major components, the two most important of which are the treatises on speech pathology and remedial principles. A section devoted to case histories, appendixes with methods of examination and functional testing and an unusually complete glossary add to the thoroughness of the presentation. Many photographs, illustrations and tables bespeak the authors' obvious aim toward exhaustive coverage of their subject.

The initiate in the pathology of speech will sense an unfamiliar terminology and will be mildly surprised at the oversimplification of anatomicophysiologic mechanisms. But there will also be noted, to his gratification, an increasing tendency toward coordination of activities on the part of the teacher of speech and the specialists in various fields of medicine, notably oral and plastic surgery, neurology, psychiatry, pediatrics and otolaryngology.

Of particular interest is the recognition of speech as an intrinsic part of the personality. Yet the authors caution against the assumption that all functional speech disorders have their basis in emotional disturbances. The chapters on dyslalias caused by deficient hearing and disorders of speech perception are especially to be commended for their clarity and their inclusion of the most recent advances in audiology.

The volume is well set up save for a rather cumbersome listing of contents in the early pages. Its chief value would seem to be as a textbook, but it contains much material of interest to physicians and particularly to specialists concerned to any extent with speech disorders.

Kompendium der parasitischen Würmer im Menschen. By Hans A. Kreis, M.D. Price, 10 Swiss fr. Pp. 136, with 70 illustrations. Basel: Benno Schwabe & Company, 1947.

Kreis has written a well arranged treatise on intestinal parasites in man. The presentation is clear even though slightly burdened by material unusual in a consideration of this subject.

The book has four main divisions: (1) a section on the structure and life cycle of helminths, pathologic changes observed in man and general remarks concerning therapy and prophylaxis, (2) a section on diagnosis of helminthiasis, (3) a special section considering the distribution, pathologic process, therapy and prophylaxis in relation to each parasite and (4) a final section dealing with the synonyms of each parasite and a tabular recapitulation of the important data presented in sections 1 and 2.

While it would be difficult for the clinician to read this book in its entirety, it should prove most valuable for frequent reference.

Hospital Care in the United States. By the Commission on Hospital Care. Price, $4.50. Pp. 609. New York: The Commonwealth Fund, 1947.

This book of 609 pages presents a study of the function of the general hospital, its role in the care of all types of illness and the conduct of activities related to patient service, with recommendations for its extension and integration for more adequate care of the American public.

Prompted by the American Hospital Association and financed by several funds, a committee made up of outstanding persons from fields which have a broad interest in health and welfare activities was independently selected to carry on the study. Such a broad subject as hospital care available to the general public could not arrive at an appraisal of each individual unit, and so the study to be made was reduced to six basic objectives. Further, because of the limitations of time and finance, one state was selected for a comprehensive study. This survey became the pattern for the other states through agencies set up within them to make their own evaluation of facilities available and to develop a plan for extension of hospital care on the basis of geographic and actual need.

The study presents a large amount of factual data, with charts and graphs on the various factors related to the problem of the care of patients in the United States. The Commission spent two years on this survey, and from all the information gathered they arrive at one hundred and eighty-one conclusions and recommendations which are so marked as to refer the reader to the detail from which each is drawn.

While some of these recommendations deal with broad problems which require collective action, there are also many which serve a double purpose in acting both as a guide and as a yardstick of the service which a general hospital should perform. The report seeks to make the general hospital the focal point for both curative and preventive health services. To accomplish this, complete care is recommended for general conditions, contagion, tuberculosis and psychiatric and chronic diseases. Considerable attention is given to education of medical and dental students and student nurses seeking to integrate the teaching in hospitals with educational institutions.

There are many other recommendations dealing with such related subjects as medical social service, physicians' offices in hospitals, public health departments, licensure of hospitals, hospital care for minority groups, financing and distribution of hospital service and, not the least important, personnel policies. Finally, specific recommendations are made in regard to the addition of beds needed and the estimated cost of providing facilities to meet the indicated need.

Time will determine the thoroughness of this report dealing with a most fundamental need—complete care for all in general hospitals equipped to render modern medical service.

Pulmonary Edema and Inflammation. By Cecil K. Drinker, M.D. Price, $2.50. Pp. 106, with 27 illustrations. Cambridge, Mass.: Harvard University Press, 1945.

This book is a collection of five lectures given at the Bowman Gray School of Medicine. These lectures represent the results of Dr. Drinker's experiments in both animal and human pulmonary physiology. It is written in an easy style, making the book delightful reading. Dr. Drinker presents clearly the physiopathologic background for the development of pulmonary edema and the serious effects of anoxia. In his discussion, the clinical implications of the underlying disturbance are always kept to the fore, making it a valuable book for the clinician. The vicious circle of anoxia, pulmonary edema and anoxia, with its insidious onset and its attendant dangers, is vividly presented. The need for early use of oxygen in conditions of deprivation of oxygen and the methods of best administering it in various circumstances are given. The clinician will find in this book the physiologic basis for much that is known of oxygen therapy.

The indications for the use of carbon dioxide with oxygen in therapy are also discussed. Mechanisms by which a variety of situations, such as posture, anesthesia and other conditions, influence pulmonary ventilation are outlined, presenting to the anesthetist a clear physiologic basis for the pulmonary disturbances occurring during anesthesia. A chapter on the physiology of respiration contains throughout clinical implications obtained from the experimental laboratory and clinical experimentation. The chapters entitled "Preventive and Therapeutic Measures in Asphyxiating Pulmonary Disease" and "Artificial Respiration" bring to the clinician valuable information on the use of oxygen and the various methods of resuscitation. A variety of respirators are listed, together with a discussion of their virtues and faults as determined by physiologic experimentation, thus bringing to the clinician a rationale for their use.

A bit of philosophy runs through the book, revealing Dr. Drinker as the true liberal, a scientist. This book should be required reading for clinicians in all fields, especially those who administer anesthesia and those responsible for oxygen therapy. Pediatricians will gain considerable help through an understanding of the physiologic basis of the methods which are employed in the resuscitation of infants and an appreciation of the need for early oxygen therapy to counteract anoxia and pulmonary edema.

Expectant Motherhood. By Nicholson J. Eastman, M.D. Second Edition. Price, $1.50. Pp. 198, with illustrations. Boston: Little, Brown & Company, 1947.

In the past fifteen years a number of books have appeared the purpose of which has been to instruct expectant mothers concerning the hygiene of pregnancy, to give them a modest amount of information about labor and to indicate what should be done to favor the normal course of the puerperium. Such a book, to be of real value to the expectant mother for whom it is written, should be concise and, above all, simple. The mother who reads it is not familiar with anatomy and physiology. She merely wants to know what is going on and what she should do to further the natural process of bringing forth a baby. Such a book should not try to tell too much, for the reader may easily be confused, or perhaps alarmed.

The little book of Dr. Nicholson Eastman, now appearing in its second edition, is an excellent example of this type of work. It is short, a little under 200 small pages, and it deals with the things in which a pregnant woman would be most interested. Descriptions and explanations are simple. The story of the growth and development of the fetus is told in language which is comprehensible to the

average patient. Diet, weight control and hygiene are simply explained, and the need for control of gain in weight is emphasized. A simple description of the process of birth occupies one chapter. A useful part of the book is the section devoted to relief of pain during labor. The discussion of this topic is most sensible.

A short section in which the Rh factor is discussed has been added. Simple instruction as to the care of the newborn baby is given, but no extended pediatric detail is attempted. The book ends with a chapter on the convalescence from labor.

This book may be warmly praised. It may be recommended by obstetricians and pediatricians to patients with confidence that the information which they get from it will be sound and in accord with today's obstetric thought. Those things which the expectant mother does not need to know, and which might alarm her, have been left out. The book has been a useful one in its first edition. The second edition should prolong its usefulness.

Penicillin Therapy, Including Streptomycin, Tyrothricin and Other Antibiotic Therapy. By John A. Kolmer, M.D. Second Edition. Price, $6. Pp. 339, with illustrations. New York: D. Appleton-Century Company, Inc., 1947.

In spite of the fact that the first edition of "Penicillin Therapy," by Dr. Kolmer, was published in 1945, because of the demand for such a text and the rapid progress in antibiotic therapy, it has been necessary for the author to revise the book. This second edition has been enlarged considerably and includes much new material and many additional illustrations. There are new chapters on the properties, administration and clinical application of the newer antibiotics, such as streptomycin, tyrothricin and streptothricin. A new chapter on antibiotic therapy and its relation to veterinary medicine will make this book a valuable tool for those interested in veterinary medicine.

The approach of the second edition of "Penicillin Therapy" is different from that of the first. In the first edition, the author discussed the various diseases from the standpoint of their bacteriologic or etiologic classifications. In the second edition, however, he explains the clinical applications of penicillin and streptomycin under the disease entities, since many of these diseases as encountered in both man and animals are caused by more than one pathogenic organism. This arrangement has made the book of greatest value to clinicians because of its value for ready reference. Even though the clinical applications of the antibiotics are presented under the classification of the disease entities, the author stresses the fact that the greatest success in obtaining the therapeutic value of the antibiotics lies in the specific bacteriologic diagnosis and in the determination of the resistance of the particular causative organism. For this reason, the chapter on practical laboratory procedures; the determination of the concentration of the penicillin and streptomycin in serum, urine, spinal fluid and other biologic materials, and the new laboratory procedures in the determination of the susceptibility of the various organisms encountered is presented in considerable detail. An effort has been made to simplify many of these procedures, so that the average clinical laboratory may be able to derive much scientific information.

Clinicians will find this book of great value in their everyday work. Dentists, veterinarians, medical and dental students and medical technologists will find many practical answers in this book to the problems they are confronted with daily. This book can be recommended fully to all.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Bornehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Asociacion de Pediatras de Cataluna

President: Dr. Emilio Roviralta, Policlinico, Platon 1, Barcelona.
Secretary: Dr. Francisco Llaurado, Via Layetana 23, Barcelona.

Associacao Paulista de Medicina, Seccao de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjorup, Dronning Louises Bornehospital, Copenhagen.

Nederlandsche Vereeninging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, c/o Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1, Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft fur Padiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Prof. Dr. Luis V. Sotelo.
Secretary: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Place: Casilla de Correos 12, La Paz, Bolivia.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

Sociedad Cubana de Pediatria

President: Prof. Augustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

Sociedad Mexicana de Pediatria

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

Sociedad de Pediatria de Concepcion (Chile)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.

Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRIA DE CORDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.) Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRIA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores Chacin, Sur 17, No. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIETE DE PEDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenida Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY
SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. John A. Toomey, City Hospital, 3395 Scranton Rd., Cleveland 9.

Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

AMERICAN HOSPITAL ASSOCIATION, MASSACHUSETTS HOSPITAL ASSOCIATION
Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

AMERICAN PEDIATRIC SOCIETY
President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN
President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

SOCIETY FOR PEDIATRIC RESEARCH
President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY
President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY
President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY
President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

NORTHWESTERN PEDIATRIC SOCIETY
President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY
President: Dr. John M. Nelson, 1558 Humboldt St., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS
Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Place: Miami, Fla. Time: October 1948.

STATE

ALABAMA PEDIATRIC SOCIETY
President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6.
Place: Montgomery, Ala. Time: September 1949.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. F. M. Meyer, 144 Golden Hill St., Bridgeport.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SECTION

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.
Place: Philadelphia. Time: Oct. 4-7, 1948.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Gerald C. O'Neil, 116 S. 49th Ave., Omaha 3.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW JERSEY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Samuel Ravenel, 371 N. Elm St., Greensboro.
Secretary: Dr. Charles Gay, 1521 Elizabeth Ave., Charlotte.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

TENNESSEE PEDIATRIC SOCIETY

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

TEXAS PEDIATRIC SOCIETY

President: Dr. Charles B. Alexander, 1716 Nix Professional Bldg., San Antonio 5.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. Thomas Gibson, 114 W. Boscawen St., Winchester.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION OF PEDIATRICS

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

WISCONSIN STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION.

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.

Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Tine: 8:30 p. m., third Thursday of each month.

BALTIMORE CITY MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore.
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Harold T. Vogel, 3420-86th St., Jackson Heights, N. Y.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

BUFFALO PEDIATRIC SOCIETY

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

CHICAGO PEDIATRIC SOCIETY

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

CINCINNATI PEDIATRIC SOCIETY

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

DALLAS PEDIATRIC SOCIETY

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Thursday of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

KNOXVILLE-OAK RIDGE PEDIATRIC SOCIETY

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2, Wis.
Secretary-Treasurer: Dr. Katharine Baird, 1411 Wauwatosa Ave., Wauwatosa 13. Wis.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

NEW YORK ACADEMY OF MEDICINE, SECTION ON PEDIATRICS

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. J. A. Gilmartin, 3708 Fifth Ave., Pittsburgh.

Secretary-Treasurer: Dr. C. J. Soecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

PORTLAND (ORE.) ACADEMY OF PEDIATRICS

President: Dr. Scott Goodnight, 1020 S. W. Taylor St., Portland 5.
Secretary-Treasurer: Dr. Carl G. Ashley, 2455 N. W. Marshall St., Portland 10.
Place: University of Oregon Medical School Library. Time: 8:00 p. m., first Monday of each month from September to June, inclusive.

QUEENS PEDIATRIC SOCIETY

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. V. E. Hrdlicka, 7424 Cromwell Dr., St. Louis.
Secretary-Treasurer: Dr. Don L. Thurston, 21 Cambridge Court, St. Louis 22.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

SAN ANTONIO PEDIATRIC SOCIETY

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.
Place: University Hospital, Ann Arbor. Time: Oct. 29-30, 1948.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRICS SECTION (NEW YORK)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).